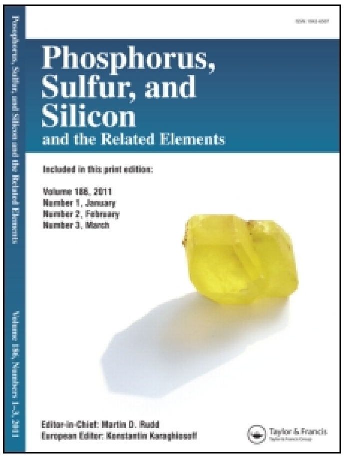

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STUDIES IN THE HETEROCYCLIC SERIES. XIV. THE CHEMISTRY AND BIOLOGICAL ACTIVITY OF NEW AZA- AND THIA-PHENOTHIAZINES, AND RELATED DIBENZOTHIAZEPINES

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Review

STUDIES IN THE HETEROCYCLIC SERIES. XIV. THE CHEMISTRY AND BIOLOGICAL ACTIVITY OF NEW AZA- AND THIA-PHENOTHIAZINES, AND RELATED DIBENZOTHIAZEPINES

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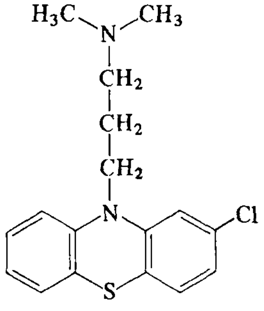
Owing to increasing demand for phenothiazine compounds both in medicine and industry, novel rings in these series have been prepared and evaluated. The benzene rings have been replaced with pyrrole, pyrazole, pyridine, pyridazine, pyrimidine, pyrazine, thiazine and triazine rings or their combinations leading to twelve new polyaza- and thia-phenothiazines. Expansion of the central thiazine ring in these systems has also been carried out. This article therefore provides a survey of the chemistry and applications of new polyaza- and thia-phenothiazine systems and their related thiazepines and thiazocines.

1 INTRODUCTION

Interest in methylene blue, Lauth's violet and related phenothiazinoid dyes led Bernthsen[1] to investigate the preparation of the parent phenothiazine ring. His success in 1883 by the simple thionation of diphenylamine opened a new chapter in the chemistry of useful heterocyclic compounds as several phenothiazine derivatives were found to have a wide variety of very useful applications. In the past, they were mainly used in the dye industry where they constitute an important class of sulfur dyes.[2-3] Additionallly, they were found to be useful antioxidants[4-6] and have also shown several chemotherapeutic effects.[7] Notable among the early phenothiazine drugs are chlorpromazine (1),[8] promethazine (phenergan) (2),[9] and diethazine (diparcol) (3)[10] which are used as tranquilizer, antihistamine and for the treatment of Parkinson's disease respectively. Several other derivatives which were prepared are also active as antiemetic,[8] antitumor,[11] smooth muscle relaxant,[12,13] antithrombogenic[12,13] diuretic,[12,14] antihistaminic,[14] anthelmintic,[15] sedative,[15] antibacterial, psychopharmacological,[16] hypotensive[17] and insecticidal agents[18] to name a few. Thus, it can be rightly concluded that phenothiazine drugs play a very important part in chemotherapy.



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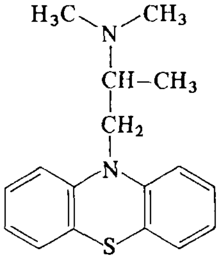

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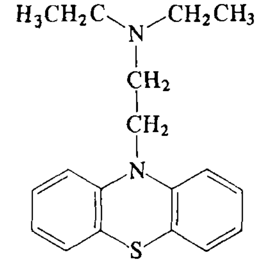

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† This article is dedicated as a tribute to Professor R. B. Woodward, the 1965 Nobel Prize-Winner in Chemistry and the author's former postdoctoral professor at Harvard, in remembrance of his kindness, encouragement and stimulating advice, and in recognition of his many outstanding accomplishments in the field of heterocyclic and natural products chemistry.

As one of the most useful heterocyclic rings so far known, extensive structural modifications of phenothiazine and its derivatives are still in progress in an attempt to improve their biological activities and to reduce the undesirable side effects. Early studies were concentrated on the synthesis of the side chain and the 10-alkylaminoalkyl derivatives. The chemistry and biological properties of phenothiazine have been reviewed many times[19–20] and more recently by Bodea and Silberg.[21] Within the last three decades several structural modifications of the phenothiazine ring itself leading to aza- and thiaphenothiazines have also been made. In two previous articles, the chemistry and the applications of nine monoaza- and four diazaphenothiazines,[22] two monothieno[1,4]benzothiazines and one dithieno[1,4]thiazine[23] were discussed. In these reports, the importance of these aza- and thia-analogs was also highlighted. The most useful compounds in these series are the derivatives of 1-azaphenothiazine[24–25] followed by 1,2-diaza-,[26] 2,3-diaza-,[27] and then 2,4-diazaphenothiazines.[28] It is therefore not surprising to observe that in many new aza- and thiaphenothiazines, there is the retention of ring nitrogen in C-1, C-2 and C-3, C-1 and C-3, C-3 and C-4 or a variation of them resulting in diaza-, triaza-, and tetraazaphenothiazines as the case may be.

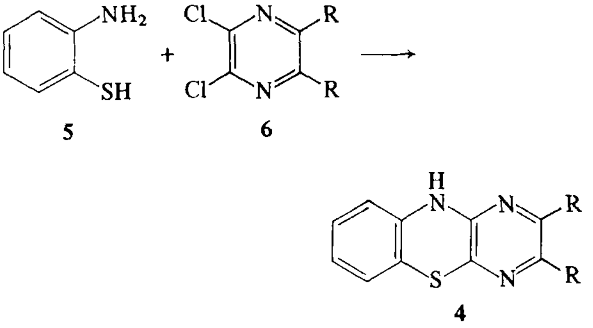
Within the last decade, thirteen new aza- and thiaphenothiazine rings and new products derived from them have been reported. These compounds have continued to show interesting chemotherapeutic effects which is probably responsible for their publications in classified literature and as patents. In this article, we wish to present a survey of the chemistry and applications of these new thia- and polyazaphenothiazines.

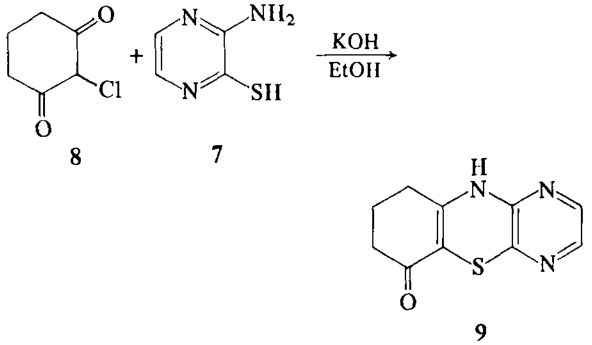
2 1,4-DIAZAPHENOTHIAZINE

In a systematic attempt to prepare all the six isomeric diazaphenothiazines, 1,2-diaza-, 2,3-diaza-, 3,4-diaza-, 1,3-diaza and 2,4-diazaphenothiazines were reported previously.[22] The synthesis of the remaining 1,4-diazaphenothiazine (4, R = H) has now been achieved.

This was accomplished[29–30] by condensing an alkaline mixture of 2-aminothiophenol (5) with 2,3-dichloropyrazine (6). Oxidation of the resulting 1,4-diazaphenothiazines (4) with 35% H_2O_2 gave the corresponding 5-dioxides.

If, on the other hand, an ethanolic sodium hydroxide solution of 3-amino-2-mercaptopyrazine (7)[31–33] is treated with 2-halocyclohexane-1,3-dione (8), 6,7,8,9-tetrahydro-1,4-diazaphenothiazin-6-one (9) was obtained.[34]



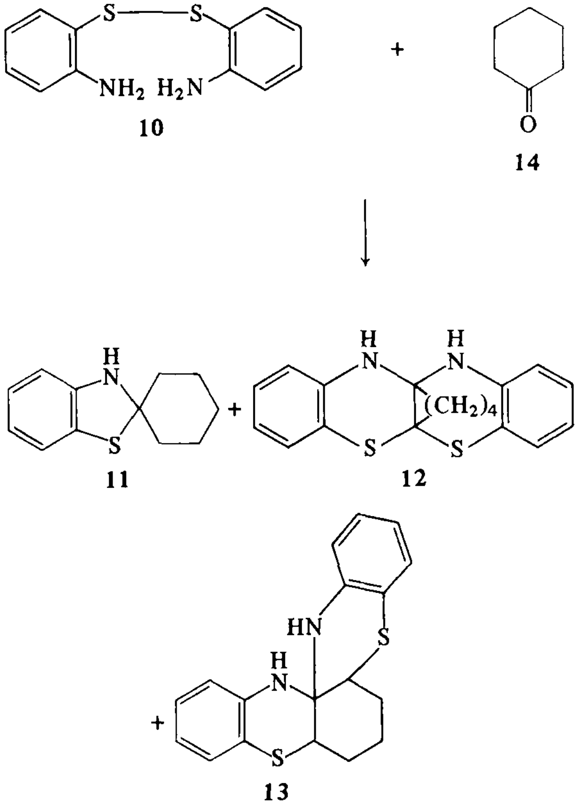


Alkylation of these 1,4-diazaphenothiazines with benzyl bromide, dimethylaminopropyl chloride and morpholinopropyl chloride in the presence of strong base afforded the corresponding 10-alkyl-6,7,8,9-tetrahydro-1,4-diazaphenothiazines.

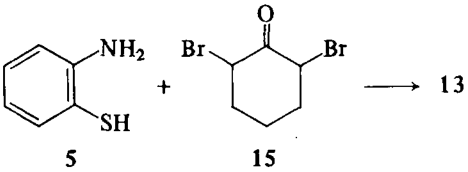
At a concentration of 100 ppm 10-(3-dimethylaminopropyl)-6,7,8,9-tetrahydro-1,4-diazaphenothiazine gave 100% control of *Staphylococcus aureus, Candida albicans* among others. 10-Benzyl-2,3-dichloro-1,4-diazaphenothiazine-5-dioxide controlled the growth of *Trichophyton mentagrophytes* at 1-10 ppm while at a concentration of 900 ppm it controlled the growth of *Candida albicans.*

3 1-AZA-4-THIAPHENOTHIAZINE

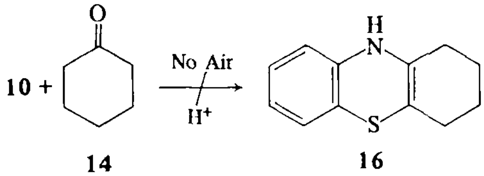
During a study of the reaction of bis-(*o*-aminophenyl) disulfide (10) with various ketones in the presence and absence of air, Carelli *et al.*[35] reacted this disulfide, 10, with cyclohexanone in the absence of air. Three major products were obtained. One of them was identified as spiro[benzothiazoline-2,1′-cyclohexane] (11).[36] The remaining two products 12 and 13 had the same molecular formula of $C_{18}H_{18}N_2S_2$ and melted at 163–164° and 201–202° respectively. They were subsequently identified as 5a,11a-butano[1,4]benzothiazino [2,3-b] [1,4]benzothiazine (**12**) and 6,7,8,8a-tetrahydro-5aH-[1,4]benzothiazino[2,3-k]phenothiazine(**13**) from a study of their infrared and nmr spectra.

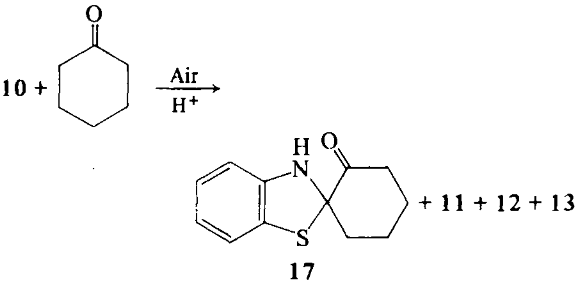


Structure 13 was confirmed by the isolation of an identical compound from the reaction of 2-aminothiophenol (**5**) with 2,6-dibromocyclohexanone (**15**).



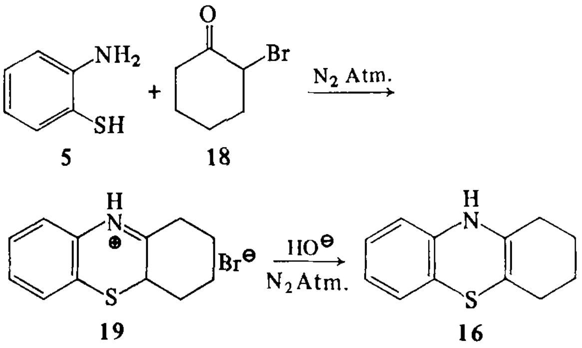
It will be noted that the reaction of the disulfide, **10**, with cyclohexanone in the absence of air did not yield the anticipated 1,2,3,4-tetrahydrophenothiazine (**16**). When the reaction was however carried out in the presence of atmospheric oxygen, an oxygen containing product, **17**, of molecular formula $C_{12}H_{13}NOS$ melting at 90-92° was reported together with the compounds, **11**, **12** and **13**. Infrared evidence showed that the oxygen in compound **17** is present in the carbonyl group. Raney-Nickel desulfurization yielded 2-anilinocyclohexanone. These reactions together with the nmr spectrum indicate that compound **17** is spiro[benzothiazoline-2,1′-cyclohexan-2′-one].





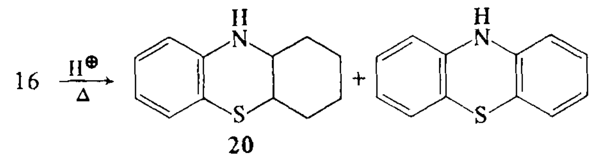
It was deduced from these and other reactions[38-39] that spirobenzothiazolinecyclohexanones often arise from autoxidation of tetrahydrophenothiazines. This observation suggests that the absence of the expected tetrahydrophenothiazine when the disulfide **10** was reacted with cyclohexanone with the exclusion of air is due to further transformation of this intermediate. It was therefore considered necessary to prepare this compound (**16**)[35] which had not been synthesized previously.

The preparation was achieved by reacting 2-aminothiophenol (**5**) with 2-bromocyclohexanone (**18**) in an inert atmosphere. 1,2,3,4a-Tetrahydro-3H-phenothiazine hydrobromide (**19**), which was obtained, was converted to 1,2,3,4-tetrahydrophenothiazine (**16**) by treatment with a base under nitrogen atmosphere followed by vacuum distillation and crystallization.



The structure of compound (**16**) which melted at 55-60° (bp. 133-135/0.01 mm), was established by a study of its infrared and nmr spectra.

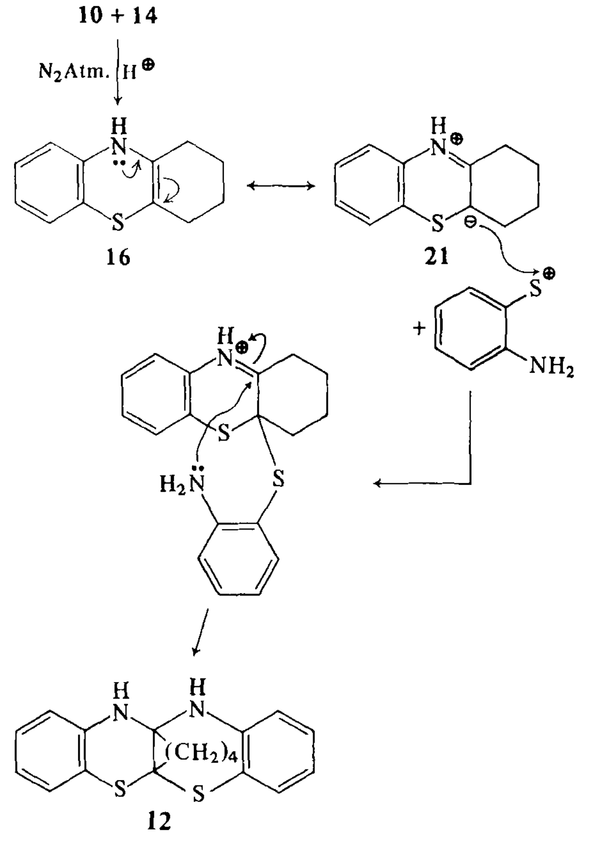
Compound **16**[35] and related compounds[39-40] were shown to have enaminic character and this property was used to rationalize its disproportionation to a mixture of 1,2,3,4,4a,10a-hexahydrophenothiazine (**20**) and phenothiazine. This enaminic property was also used to establish the mechanism of transformation of compounds **10** and **14** to **12** and **13**.

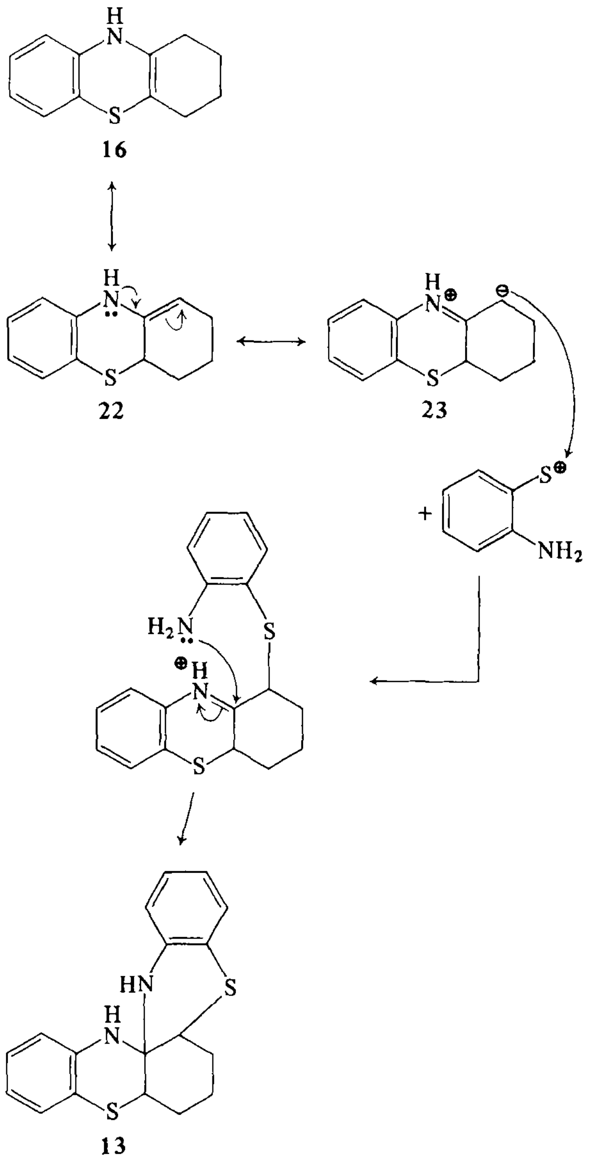


The conversion of the disulfide (**10**) and cyclohexanone (**14**) mixture to compounds **12** and **13** was shown to proceed via the 1,2,3,4-tetrahydrophenothiazine intermediate (**16**). No reaction was however observed if this intermediate was treated with 2-aminophenol but when compound **16** was made to react with **10** under the original reaction conditions (acid medium and absence of air) the reaction proceeded smoothly and both compounds **12** and **13** were obtained.

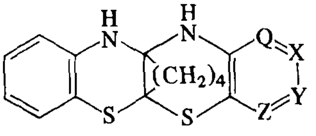
The formation of compound **12** was therefore explained by a mechanism involving the heterolytic cleavage of the disulfide bond by an attack of the β-enaminic carbonion (structure **21**). This was followed by intramolecular cyclization by the addition of the amino group of the cleaved disulfide to the iminium cation of the tetrahydrophenothiazine intermediate.

By a similar mechanism the formation of compound **13** would imply the partial existence of **16** in the tautomeric form **22** which was not observed in the nmr spectrum.





Having established the intermediacy of 1,2,3,4-tetrahydrophenothiazine in the formation of 1-aza-4-thiaphenothiazines of type **12**, it will be interesting to react it with disulfides of *o*-aminopyridine, *o*-aminopyridazine, *o*-aminopyrimidine and *o*-aminopyrazine to obtain additional aza-, and diaza- variations of 1-aza-4-thiaphenothiazines of types **24**.



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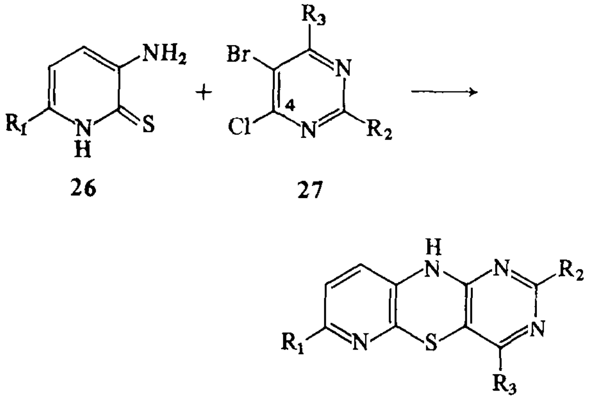
(a) Q = Z = N, X = Y = CH
(b) Q = X = N, Y = Z = CH
(c) Q = Y = N, X = Z = CH
(d) X = Y = N, Q = Z = CH
(e) X = Z = N, Q = Y = CH
(f) Z = Y = N, Q = X = CH

4 1,3,6-TRIAZAPHENOTHIAZINE

All the earlier reports on the aza analogs of phenothiazine were concerned with the chemistry and biological properties of only the monoaza- and diazaphenothiazines —there was no report whatsoever on any of the twenty-four isomeric triazaphenothiazine systems. In 1973, however, we ventured into the synthesis of the first set of compounds in these series and successfully achieved the preparation of 1,3,6-triazaphenothiazine (**25**) derivatives thereby opening this new chapter on phenothiazine chemistry.[41]

These compounds were obtained in yields varying from 11% to 95% by acid catalysed condensation of 3-aminopyridin-2(1H)-thiones (**26**)[42] with 4,5-dihalogenopyrimidines (**27**).[43]



26 **27**

25

Optimum yields were obtained in dilute acid media in which the ring nitrogens of pyridine and pyrimidine were preferentially protonated. Quarternization of these ring nitrogens would enhance the nucleophilicity of 3-NH_2 group (structure **26**) and the susceptibility of C-4 in structure **27** to nucleophilic attack. In most cases, cyclization proceeded smoothly without rearrangement.

Similar reactions were carried out using 4-halogenopyrimidines in which the 5-position is unsubstituted. The lack of a reactive group in C-5 would therefore prevent cyclization. It was found that in all cases the corresponding diarylamines referred to as "open" analogs were obtained in satisfactory yields. Several derivatives of these "open" and "closed" 1,3,6-triazaphenothiazines were prepared and characterized.

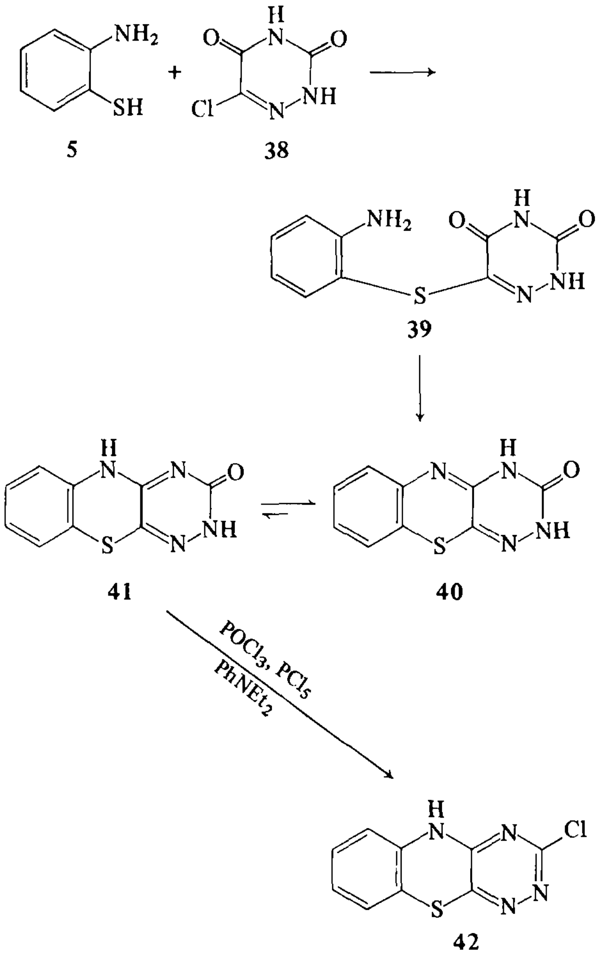
These 1,3,6-triazaphenothiazines were tested in mice and rats for their effects on the central nervous system. The test results show that the derivatives studied have appreciable CNS-depressant activities. All investigational compounds had antipyretic activity. They decreased body temperature in some cases by as much as 1.9° compared to 0.8° in chlorpromazine. In tests for anticonvulsant activity, only 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine prolonged significantly the onset of convulsion due to strychnine thereby exhibiting anticonvulsant activity. Only 2,4-dichloro-7-methoxy-1,3,6-triazaphenothiazine had a slight influence on pentylenetetrazole induced convulsions. Some correlations based on structure-activity relationships were also made.[44]

5 1,3,4-TRIAZAPHENOTHIAZINE

In addition to the reports on 1,3,6-triazaphenothiazines, Kaji and his co-workers[45–47] have also reported the synthesis of another triazaphenothiazine ring system. When 6-halogeno-1,3,4-triazine-3,5(2H,4H)-dione (**38**) was refluxed in an alkaline solution of 2-aminothiophenol (**5**), 6-(2-aminophenylthio)-1,3,4-triazine-3,5(2H,4H)-dione (**39**) was obtained. Cyclization of the diaryl sulfide, **39**, was achieved by refluxing in acetic acid for 1.5 hours. This led to 92% yield of 1,3,4-triazaphenothiazine-2(1H)-one (**40**).

Compound **40** was converted through the tautomer **41** to the chloroderivative (**42**) by the action of phosphorus oxychloride and phosphorus pentachloride in the presence of diethylaniline.[47]

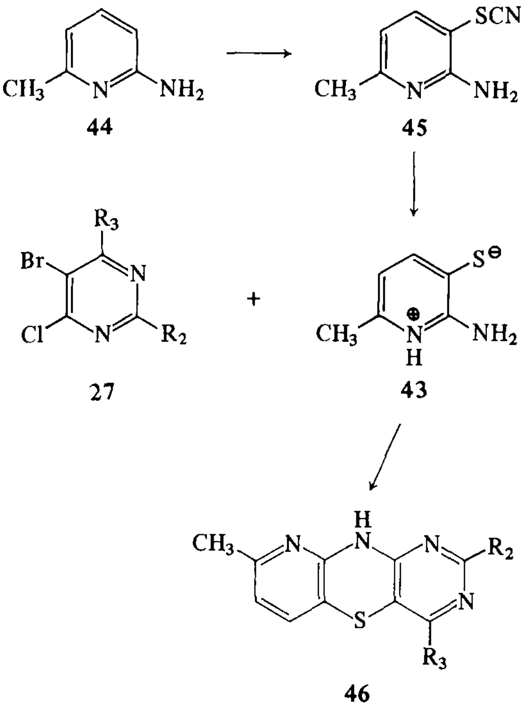
A few other side chain derivatives particularly the 3- and 10- aralkyl derivatives were also reported but no reports on the biological properties have however been made so far.

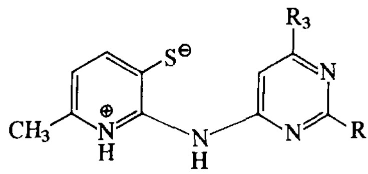


6 1,3,9-TRIAZAPHENOTHIAZINE

The third isomeric triazaphenothiazine[48] was recently reported by acid catalysed condensation of 3-mercapto-2-aminopyridine (**43**) with 4,5-dihalogenopyrimidine (**27**). The precursor *o*-aminomercaptopyridine (**43**) was obtained by Kaufmann's thiocyanation[49] of 2-amino-6-methylpyridine followed by base catalysed hydrolysis of the resulting 3-thiocyanato derivative[42] and acidification. Thus when the *o*-aminomercaptopyridine **43** was treated with 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**27**, $R_2 = R_3 = OCH_3$) in dilute sulfuric acid, 68% yield of 2,4-dimethoxy-8-methyl-1,3,9-triazaphenothiazine, **46**, was isolated. Similar products were obtained if compound **27** were replaced with 4-chloro-5-nitropyrimidines.

The "open" analogs were also prepared by similar acid catalysed reactions, using chloropyrimidines in which the C-5 position is unsubstituted. The fact that such reactions with 2-amino-3-mercaptopyridine gave in all cases, the corresponding 6-(3-mercapto-6-methyl-2-pyridyl)pyrimidylamines (**47**) is an evidence for the assigned structures.[50]





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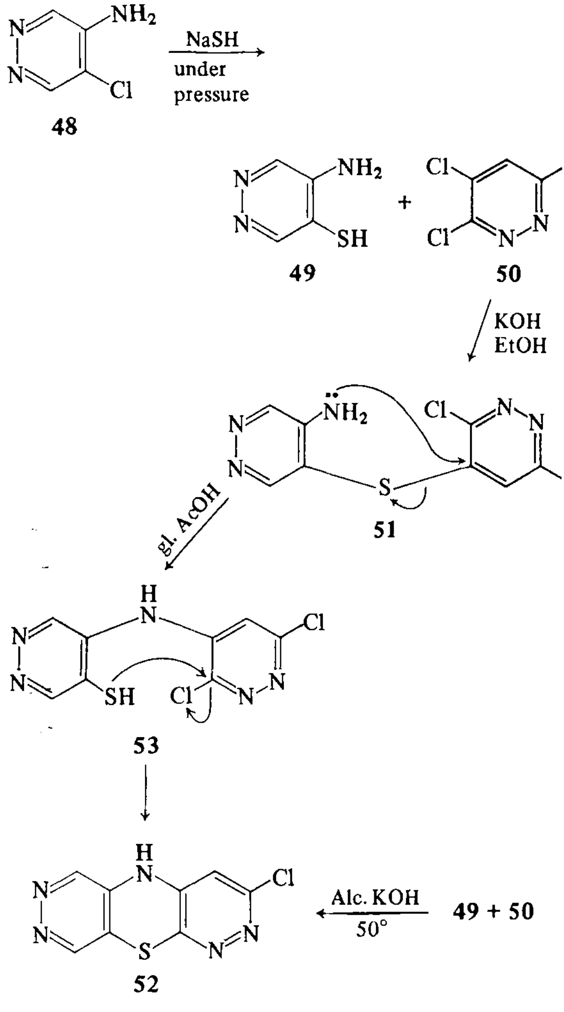
In tests with mice and rats, these derivatives of 1,3,9-triazaphenothiazine showed CNS-depressant activities in doses of 1-4 mg/kg i.p. They also showed antipyretic activities. None of the compounds, when protected against strychnine and maximal electroshock, induced seizures, however 2-amino-4-chloro-8-methyl-1,3,9-triazaphenothiazine prolonged significantly the onset due to maximal electroshock thus showing an appreciable anticonvulsant activity in mice.[44]

7 2,3,6,7-TETRAAZAPHENOTHIAZINE

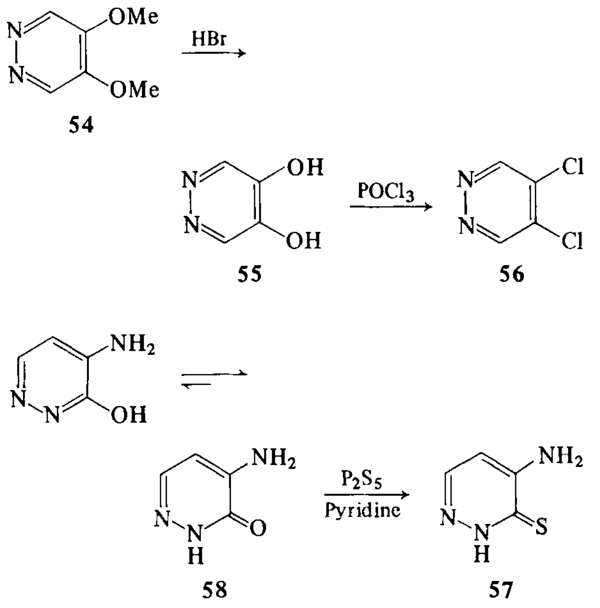
Replacement of the benzene rings in phenothiazine with pyridazine leading to tetraazaphenothiazines was recently accomplished by Wise and Castle[51] who successfully synthesized five out of thirty-five possible isomeric tetraazaphenothiazine rings. This work can be regarded as the greatest single contribution to the chemistry of azaphenothiazines in modern times.

In these reactions, 4-amino-5-chloropyridazine (**48**)[52] was converted to 4-aminopyridazine-5-thiol (**49**) in 58% yield by heating with sodium hydrosulfide under pressure. This product was then treated with 3,4,6-trichloropyridazine[53-54] (**50**) at −10° to −5° in ethanolic sodium hydroxide. The resulting dipyridazinyl sulfide (**51**) was refluxed in the presence of glacial acetic acid and gave 8-chloro-2,3,6,7-tetraazaphenothiazine (**52**), mp. 234-235°.

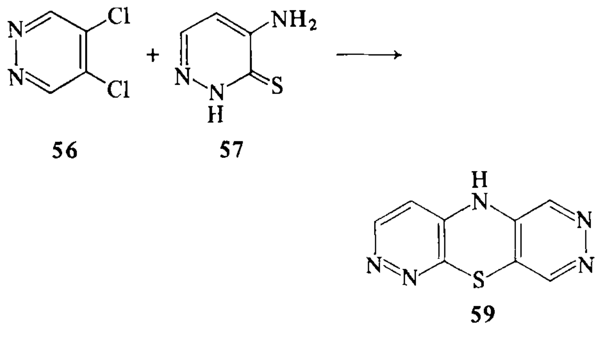


The conversion of 4-(5′-aminopyridazinyl-4′-thio)-3,6-dichloropyridazine (**51**) to the tetraazaphenothiazine, **52**, was rationalized as proceeding via Smiles rearrangement followed by cyclization. Such acid catalysed Smiles rearrangement reactions have been well established.[22] The same product (**52**) was also obtained by heating the starting materials, **49** and **50**, at 50° for 3 hours in ethanolic KOH.

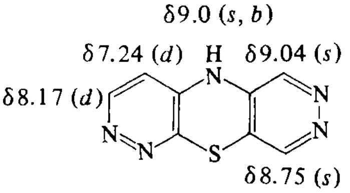
In order to establish the structure of this tetraazaphenothiazine, (**52**), the synthesis of the parent compound was attempted. 4,5-Dimethoxypyridazine (**54**)[55] was converted to pyridazine-4,5-diol (**55**) in 89% yield by refluxing in 48% hydrobromic acid. Chlorination with phosphorus oxychloride gave the 4,5-dichloropyridazine, **56**, in 61% yield. The second reactant, 5-aminopyridazin-6(1H)-thione (**57**) was obtained in 62% yield by reacting 5-aminopyridazine-6(1H)-one (**58**)[56] with phosphorus pentasulfide in pyridine.



By stirring a mixture of compounds **56** and **57** at room temperature in the presence of alcoholic potassium hydroxide, 2,3,6,7-tetraazaphenothiazine, **59**, was isolated in 55% yield. It is a white compound melting at 184-185°.



The infrared spectrum showed an NH absorption at 3380-3335 cm^{-1}. The ultraviolet spectrum had a maximum absorption band at 251 nm characteristic of phenothiazinoid systems.[41, 50] Its nmr signals were rationalized as follows:



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d = doublet, b = broad, s = singlet.

Compound **59** is the only possible product of molecular formula $C_8H_5N_5S$ obtainable from the base-catalysed reaction of compounds **56** and **57** irrespective of whether the reaction takes place with or without rearrangement. Dechlorination of compound **52** with palladized charcoal also led to the parent compound **59** in 55% yield.[51] This reaction shows that compound **52** is a derivative of the parent ring, **59**. Thus compound **52** is 8-chloro-2,3,6,7-tetraazaphenothiazine. Condensation with sodium methoxide in methanol under pressure led to 53% yield of the 8-methoxyderivative.

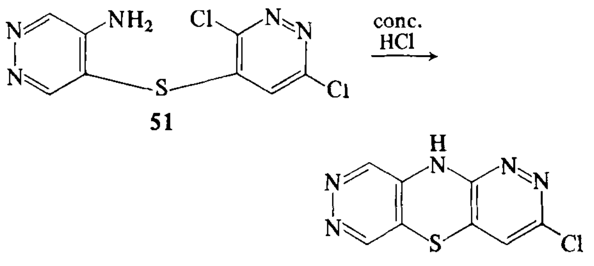
10-Alkylation of these 2,3,6,7-tetraazaphenothiazines was accomplished by reaction with sodamide followed by the addition of 3-diethylaminopropyl, 2-dimethylaminoethyl, 2-diethylaminoethyl and 2-morpholinoethyl halides. Pharmacological evaluation of these potential psychopharmacological agents is yet to be carrried out.

8 1,2,7,8-TETRAAZAPHENOTHIAZINE

It was also reported by Wise and Castle that if 4-(5′-aminopyridazinyl-4′-thio)-3,6-dichloropyridazine (**51**), obtained by base catalysed condensation of **49** and **50** were treated with concentrated hydrochloric acid, a chlorotetraazaphenothiazine[51] melting at 256-257° was obtained. Two structures are possible namely (i) structure **52** obtained via Smiles rearrangement and (ii) structure **60** obtained by direct cyclization.

As the properties of the isolated product are different from those of compound **52** obtained by refluxing **51** in glacial acetic acid, it was therefore identified as 3-chloro-1,2,7,8-tetraazaphenothiazine (**60**).

The 3-methoxyderivative was obtained in 64% yield by reaction with methanolic sodium methoxide under pressure. The pharmacological properties of these derivatives have not been reported yet.



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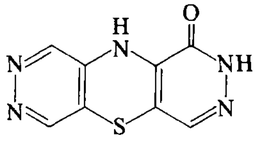
60

9 2,3,7,8-TETRAAZAPHENOTHIAZINE

By using various isomers of o-aminomercaptopyridazine and dichloropyridazine, other dipyridazino[1,4] thiazines were obtained in good yields. A derivative (**61**) of 2,3,7,8-tetraazaphenothiazine was obtained by base-catalysed reaction of compound **49** with 4,5-dichloropyridazin-6[1H]-one (**62**) at 0° for 24 hours.[51] In order to decide whether the product of this reaction is 2,3,7,8-tetraazaphenothiazin-1[2H]-one (**63**) or 2,3,7,8-tetraazaphenothiazine-4(3H)-one (**64**) further experimentation was deemed necessary.



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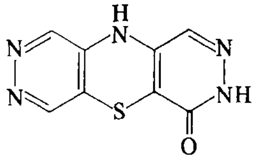
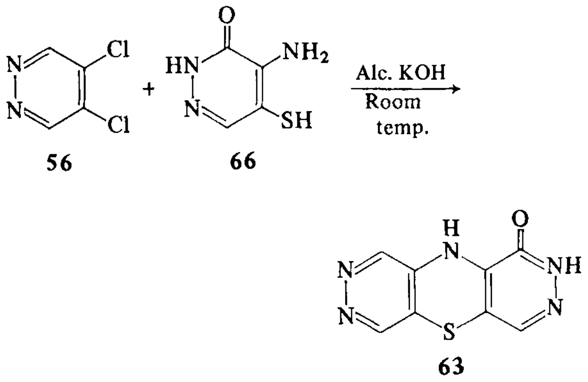
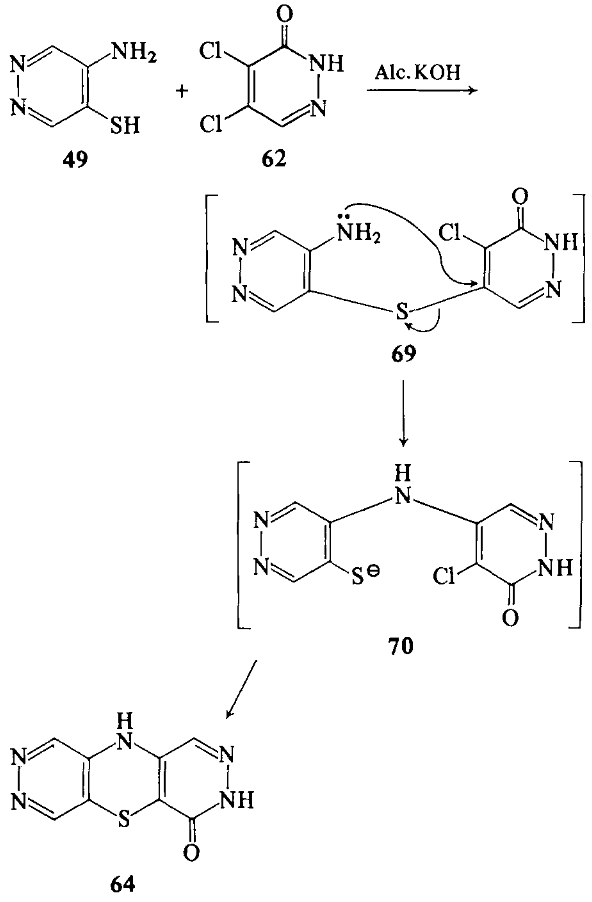


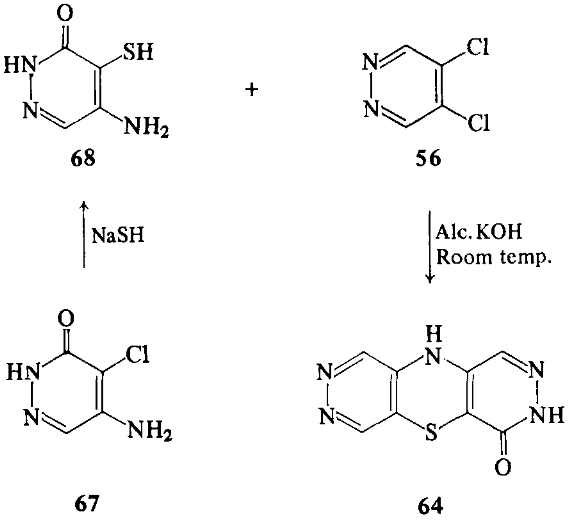
64

Compound **63** was prepared unequivocally by converting 5-amino-4-chloropyridazin-6(1H)-one (65)[57] to 5-amino-4-thiopyridazin-6(1H)-one (**66**) by the action of sodium hydrosulfide under pressure at 160°. This was followed by the action of compound **56** in ethanolic potassium hydroxide at room temperature. The tetraazaphenothiazinone **63** thus obtained is the only possible product of this reaction owing to the symmetry of compound **56**. This product possessed properties different from those of compound **61**. Thus compound **61** was assigned structure **64**.

Confirmatory evidence of structure was obtained by unequivocal synthesis from a mixture of compound **56** and 4-amino-5-thiopyridazin-1H-one which was obtained by condensation of 4-amino-5-chloropyridazin-6[1H]-one with sodium hydrosulfide under pressure. Again the only product of this reaction had both physical and chemical properties which were identical with those of compound **61** whose structure is therefore confirmed as **64**. The reactions leading to this

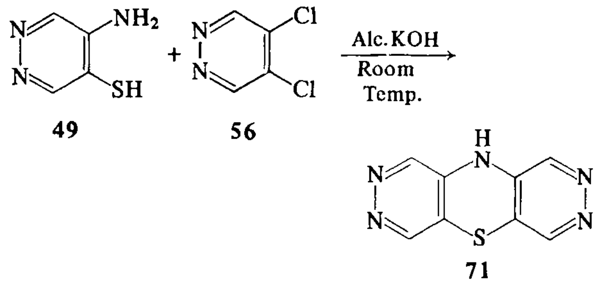




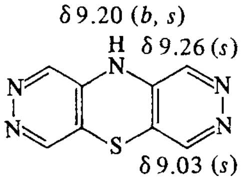


product was rationalized as proceeding *via* the formation of the diaryl sulfide, **69**, followed by Smiles rearrangement to the diarylamine **70** and base catalysed cyclization yielding the tetraazaphenothiazine, **64**. The exceptional reactivity of the 4-halogen atom can be rationalized if it is regarded as an activated vinyl chloride such as those described by Benson and Pohland.[58]

The unsubstituted 2,3,7,8-tetraazaphenothiazine (**71**) was obtained in 66% yield by treating compound **49** with **56** in the presence of alcoholic KOH at room temperature.



It is colorless solid melting at 167–168°. The ir spectrum had an NH absorption at 3380–3350 cm^{-1}. Owing to the equivalence of C-1 and C-9 positions on one hand and C-4 and C-6 positions on the other hand there are three peaks in the nmr spectrum interpreted as shown in the structural diagram.



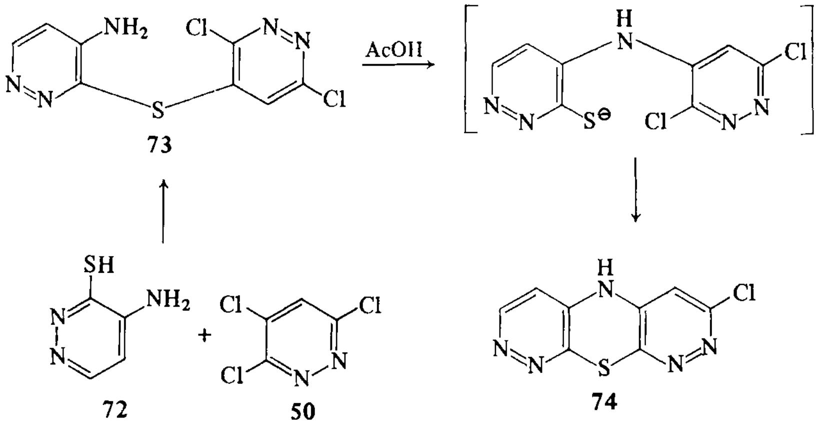
s = singlet, *b* = broad.

71

Many derivatives of this ring including the 10-diakylaminoalkyl derivatives of pharmacological interest were also prepared.

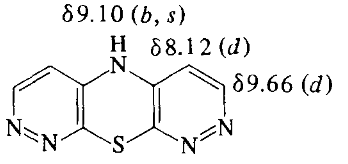
10 3,4,6,7-TETRAAZAPHENOTHIAZINE

When a mixture of 5-aminopyridazin-6[1H]-thione (**72**) and 3,4,6-trichloropyridazine (**50**) was stirred at −10° for 24 hours, a 31% yield of 4-(4′-aminopyridazinyl-3′-thio)-3,6-dichloropyridazine (**73**) was obtained.[51]

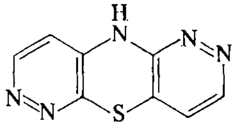


The action of acetic acid on this dipyridazinyl sulfide at 90° for 3.5 hours caused rearrangement to the diarylamine intermediate followed by cyclization. 2-Chloro-3,4,6,7-tetraazaphenothiazine (**74**) melting at 183–184° was obtained in 47% yield.[51]

The parent compound, 3,4,6,7-tetraazaphenothiazine (**75**) was obtained in 60% yield by stirring, for 24 hours, an alcoholic mixture of compound **72** and 3,4-dichloropyridazine[59] (**76**) in the presence of potassium hydroxide. It is a crystalline compound melting at 179–180°. Structural assignment was based on the similarity of the uv spectrum with that of compound **74**. Further evidence of structure was provided by the nmr spectrum which showed only three groups of peaks due to the symmetric nature of the molecule along the central ring nitrogen-sulfur axis.



75



77

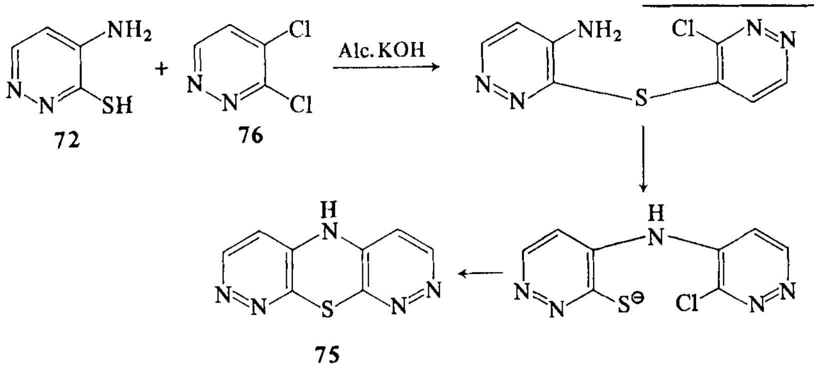
s = singlet; b = broad

The alternative structure **77** would be expected to give a more complex spectrum due to lack of symmetry The similarity of the uv spectrum of this compound with that of compound **74** is an evidence for the structure of **74** and for the postulated rearrangement of the dipyridazinyl sulfide **73**.

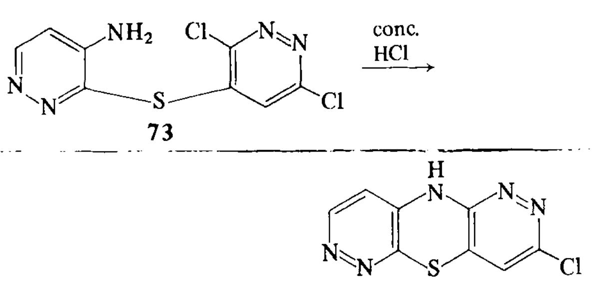
No reprot has, so far, been made on the biological properties of these 3,4,6,7-tetraazaphenothiazine.

11. 1,2,6,7-TETRAAZAPHENOTHIAZINE

Utilizing the case of cyclization of suitably substituted diaryl sulfides, Wise and Castle heated the dipyridazinyl sulfide **73** in concentrated hydrochloric acid at 90° for



4 hours. A product different from 2-chloro-3,4,6,7-tetraazaphenothizaine (**74**) was isolated in 61% yield. It melted at 256–258° and the uv spectrum is different from those of compounds **74** and **75**. The compound was therefore identified as 3-chloro-1,2,6,7-tetraazaphenothiazine (**78**).[51]



73

78

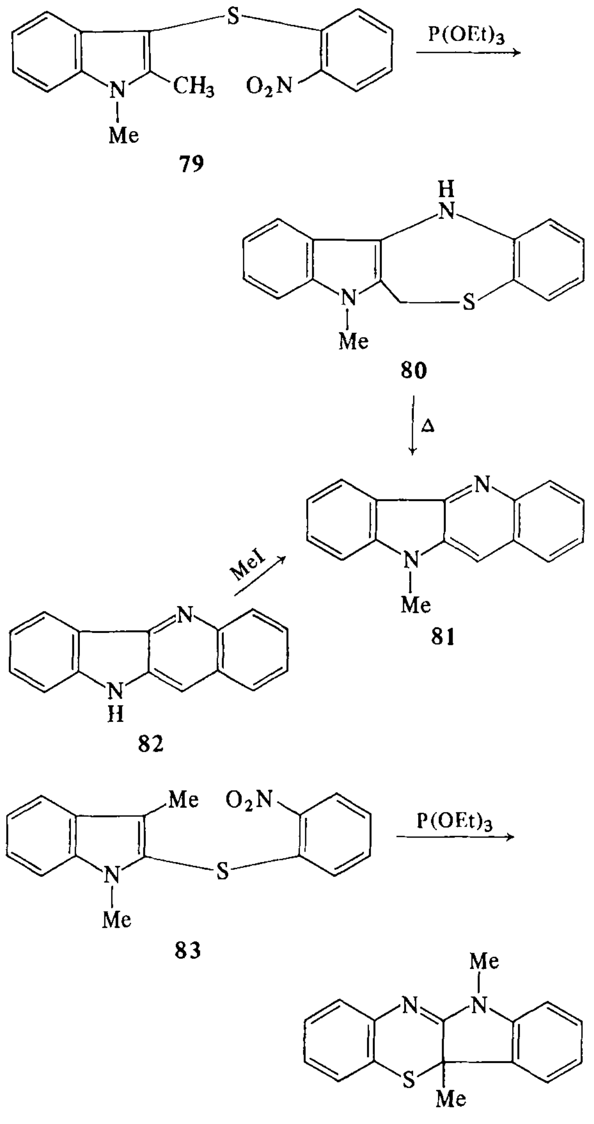
The pharmacological evaluation of this compound has not been reported yet.

12 INDOLOBENZO[1,4]THIAZINES

While studying the deoxygenation of indolyl *o*-nitrophenyl sulfides with triethyl phosphite, a variety of products which include novel phenothiazine-type compounds was reported by Jackson, Johnston and Shannon.[60] When the sulfide **79** was mixed with triethyl phosphite under reflux for 3 hours in a nitrogen atomsphere, the dihydrobenzothiazepine **80** (mp 186°) was produced in 34% yield. Heating this product above its melting point led to the loss of hydrogen sulfide and the formation of the indoloquinoline, **81**. Compound **81** is identical with the product of methylation of the known indolo[3,2-b]quinoline, **82**.[61]

On the other hand if these reactions were repeated using the isomeric 2-indolyl *o*-nitrophenyl sulfide, **83**, the indolobenzothiazine **84** was reported in 70% yield. Evidence for the assigned structure **84** was provided by an unequivocal synthesis starting with the 2-indolone, **85**. Condensation of compound **85** with *o*-nitrobenzene sulfenyl chloride (**86**) in THF led to the diaryl sulfide **87**. Reduction of the nitro-group with sodium dithionite ($Na_2S_2O_4$) in aqueous ethanol afforded the *o*-amino derivative, **88**, which cyclized by intramolecular condensation in *p*-toluene sulphonic acid to yield the indolobenzothiazine **84**. This compound had identical properties with the phosphite deoxygenation product of **83**.

Phosphite deoxygenation of 3-(N-methylindolyl) *o*-nitrophenyl sulfide, (**89**) under similar conditions afforded the spiro-oxindale, **90**, in 15% yield. On the other hand, if this reaction is worked up as rapidly as possible a solid mixture of compound **90** and another compound **91** which is unstable in air was produced. Compound **91** was identified as an isomeric indolobenzothiazine. The conversion of **91** to **90** in the presence of atmospheric oxygen was quite rapid but could be followed spectroscopically in the uv cell where the change of maximum absorption from 265 nm as in **91** to 256 nm and the appearance of another maximum at 310 nm as in compound **90** could be measured. The half life of compound **91** was reported to be approximately 3 minutes. The instability[62] of 2,3-disubstituted indoles to atmospheric oxygen is not



79

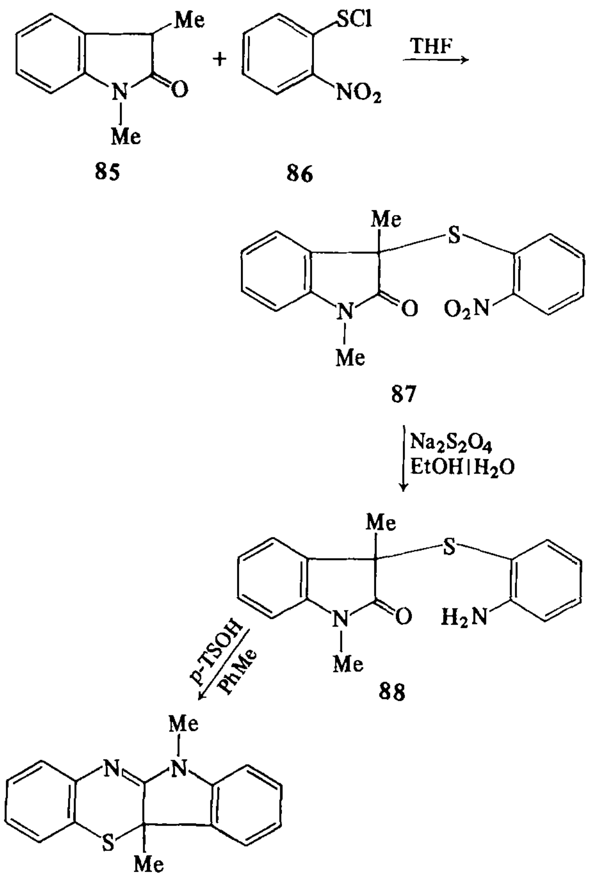
80

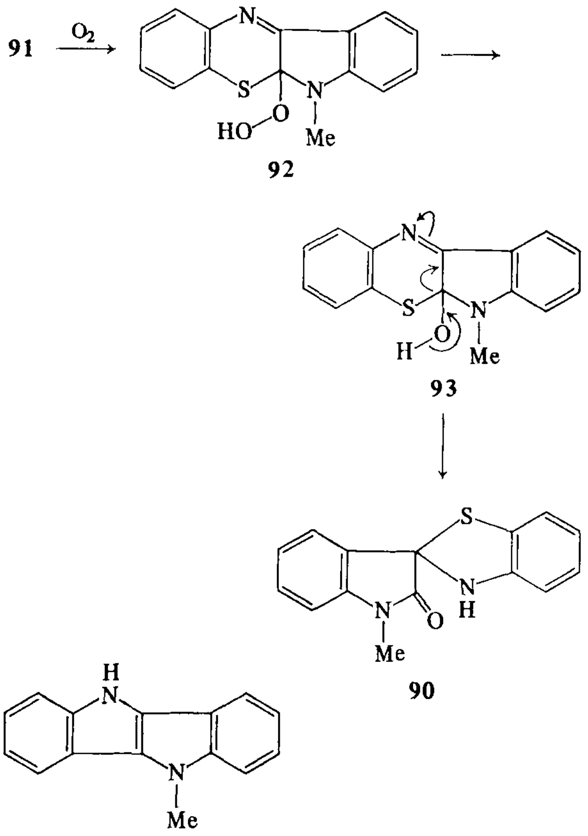
81

82

83

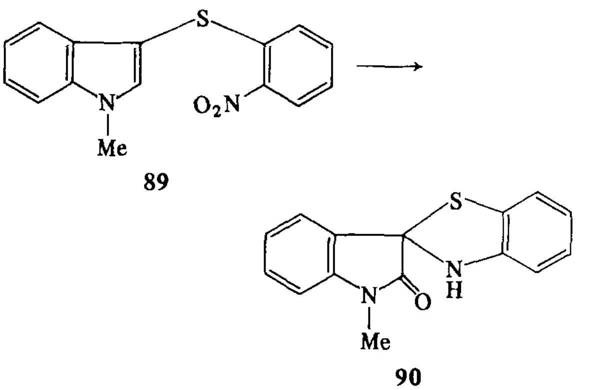
84

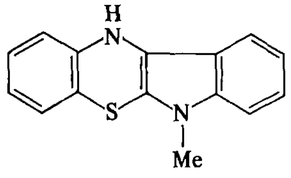




new and the transformation of the indolobenzothiazine **91** to the spiro-oxindole **90** has been rationalized as proceeding *via* an attack of oxygen at the 2-position of the indole ring leading to 2-hydroxylation. An intramolecular rearrangement of the intermediate (**93**) led to the stable spiro-compound **90**. Desulfurization of **91** with copper bronze[63] in 1,2,4-trichlorobenzene gave trace amounts of compound **94**. This is an evidence for the assigned structure.

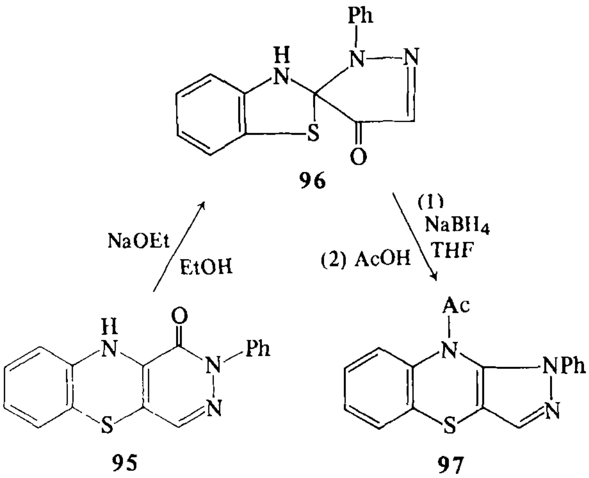
Thus phosphite deoxygenation of indolyl *o*-nitrophenyl sulfides is a successful route to indolobenzothiazines, the instability of some of these rings notwithstanding. The pharmacological evaluation of these new phenothiazine compounds has not been reported.




91

13 PYRAZOLO[4,5-b] [1,4] BENZOTHIAZINE

It was found by Kaki and Suzuki that 2-phenyl-2,3-diazaphenothiazin-1(2H)-one (**95**)[64] could be converted to the spiro-compound spiro(1-phenyl-4(5H)-pyrazolone-3,2-benzothiazoline) (**96**) by the action of sodium



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in ethanol followed by chromatography (SiO_2). Borohydride reduction of this spiro-compound in THF followed by treatment with 80% acetic acid gave 9-acetyl-1-phenylpyrazolo[4,5-b][1,4]benzothiazine (97).[65]

Several derivatives of this pyrazolobenzothiazine ring were prepared and tested in laboratory animals. Most of them were found to have psychotropic activity in animals.[65]

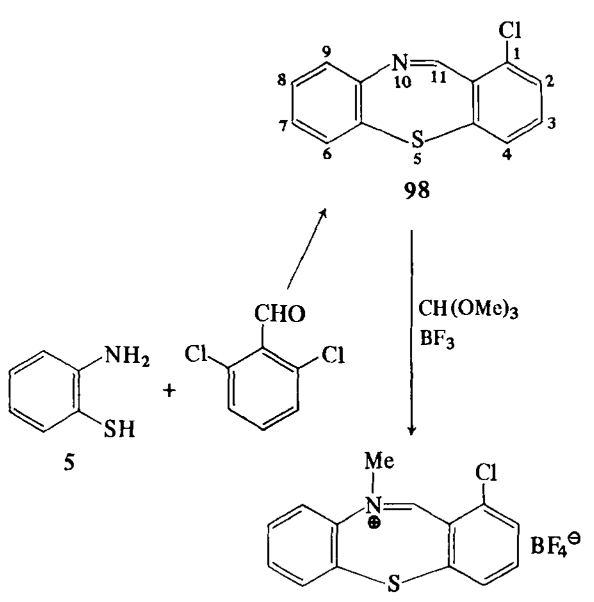
14 DIBENZO[1,4]THIAZEPINES AND RELATED COMPOUNDS

The annular analogs of phenothiazine discussed thus far are those leading to modifications of the dibenzo groups either by incorporation of annular nitrogen and sulfur atoms or by replacing them with other heterocycles. Further modifications can however be made by expansion of the central 1,4-thiazine ring while at the same time retaining the central ring heteroatoms in 1,4-positions. The latter modified structures will lead to dibenzo[1,4]thiazepine and dibenzo[1,4]thiazocine structures and their related aza- and thia- analogs.

A large number of these heterocyclic rings have now been synthesized and examined for their pharmacological properties. Owing to their high biological activities, interest in these modified phenothiazine heterocycles has grown rapidly and is posing a big challenge to the traditional phenothiazine chemistry. Because of the structural relationship between these compounds and phenothiazine, we shall include in this report the chemistry and biological effects of the novel rings in these series particularly their aza- and thia- analogs.

15 DIBENZO[*b*,*f*][1,4]THIAZEPINES

1.Chlorodibenzo[*b*,*f*][1,4]thiazepine (**98**) was prepared in 50% yield by condensing 2-aminothiophenol (**5**) with 2,6-dichlorobenzaldehyde in fused 2-methylimidazole.[66] Compound **98** was transformed into the 10-methyl-derivative and isolated as the tetrafluoroborate salt by the action of trimethyl orthoformate (**99**) in the presence of boron trifluoride at room temperature. When treated with sodium cyanide in dimethyl sulfoxide at room temperature, compound **100** was converted to 11-cyano-10-methyl-10,11-dihydrodibenzo[*b*,*f*][1,4]-thiazepine (**101**) in 70% yield.



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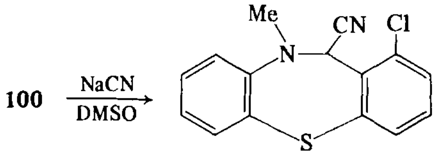
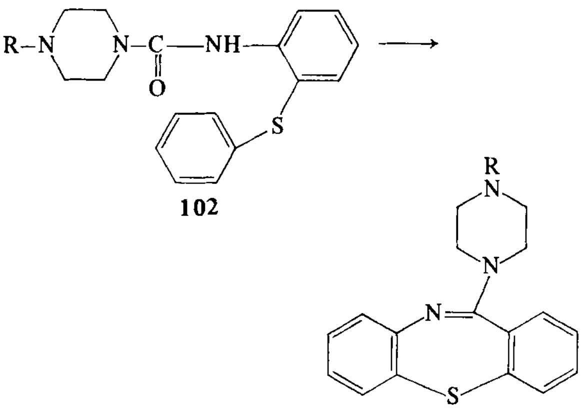


101

By ring-closure dehydration of the amides 1-piperazinecarboxylic acid *o*-phenylthioanilide (**102**) using phosphorus oxychloride, good yields of 11-piperazinyldibenzo[*b*,*f*][1,4]thiazepines (**103**) were obtained.[67] Cyclization of 4-(2-pyridylmethyl)-1-piperazinecarboxylic acid *o*-phenylsulfonylanilide (**104**) in the presence of orthophosphoric acid and phosphorus oxychloride led



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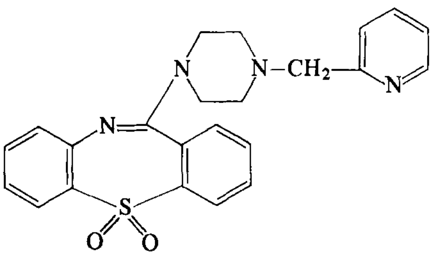
103

to the corresponding 5-dioxide **105**.[68] Beckmann rearrangement of 10-(hydroxyimino)thioxanthene 5-dioxide led to dibenzo[*b,f*][1,4]thiazepin-10-one-5,5-dioxide (**106**) in satisfactory yields. Michael addition of acrylonitrile to compound **106** followed by hydrolysis of the resulting 10-(2-cyanoethyl)-derivative and cyclization with phosphorus oxychloride gave the dibenzopyridothiazepinedione-5-dioxide (**107**) which was converted to 1,2,3,4-tetrahydrodibenzo-[*c,k,l*][1,4]-diazepino[2,1-*c*][1,4]thiazepine-3,13-dione-8,8-dioxide (**108**)[69] by the action of sodium azide in orthophosphoric acid. Several 1-, 2-, 3-, 4-, 7-, 8-, 10- and 11-substituted dibenzo[*b,f*][1,4]thiazepines and their 5-dioxides were also reported.[70-80]



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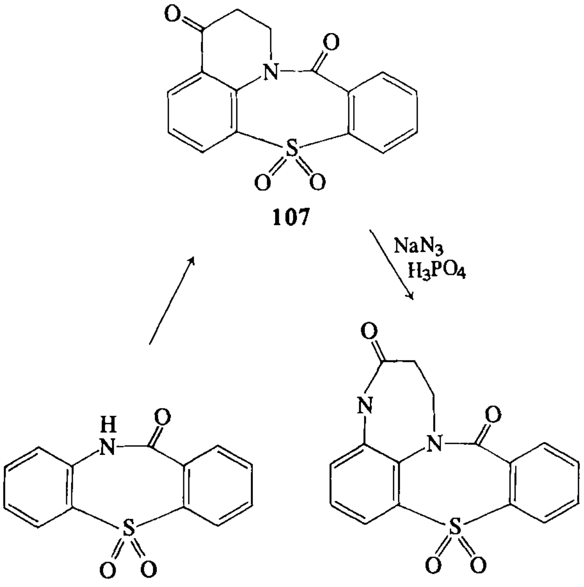

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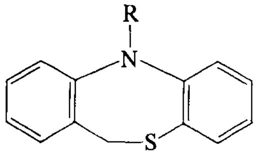
108

The biological properties of these compounds were extensively investigated in birds and mammals by several workers. Strong antihistaminic,[80] anti-depressant,[72, 75, 80, 81] antiasthma,[80] antiallergic,[8] anti-phlogistic[67] analgesic,[68, 77, 78] cholesterol depressant,[68] antiinflammatory,[68, 77] antiartesclerotic,[68] sedative,[71, 75] neuroleptic,[71] neurotropic antidepressant,[71] antiemetic,[71, 75] anxiolytic,[72] tranquilizing,[75] hypochesteremic,[77, 78] psychotropic,[77] bactericidal,[79] and fungicidal[79] activities were exhibited by these derivatives. In the 10-aminoalkylcarboxylate derivatives which showed CNS activities, the LD$_{50}$ in mice on i.p. or oral application is 75-500 mg/kg or 300-2000 mg/kg respectively.[82]

16 DIBENZ[*b,e*][1,4]THIAZEPINE

The related dibenz[*b,e*][1,4]thiazepines (**109**) were prepared by methods similar to those described in the preceding section. Several derivatives which were prepared were tested in laboratory animals in order to determine their pharmacological usefulness. Reports show that these dibenzthiazepines are useful microbicides,[83] surface disinfectants,[83] central nervous system stimulants,[84] muscle relaxants,[84] tranquilizers,[85-87] sedatives,[85] antidepressants,[86, 87] antiarrhythmic and antibacterial agents.[88] At 1 x 10^{-3}-10^{-1}% solutions, some 10-alkylamino derivatives completely eliminated *S. aureus* and T. *Mentagrophytes.*[88] In doses varying from 20-200 mg per day, certain N-alkylaminoalkyl-derivatives are sedatives and hypotensive agents.[89]



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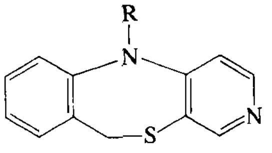
17 BENZOPYRANO-, PYRIMIDINO- AND THIAZINO[1,4]THIAZEPINES

Systems in which one of the benzo groups is replaced by pyridine (**110**)[90] and benzopyran[91] rings (**111**) have also



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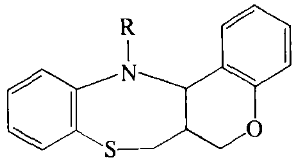
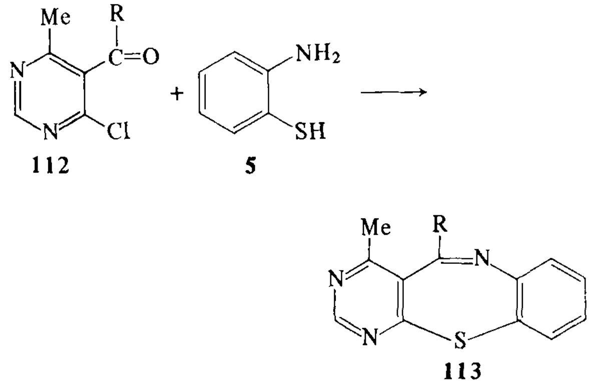


111

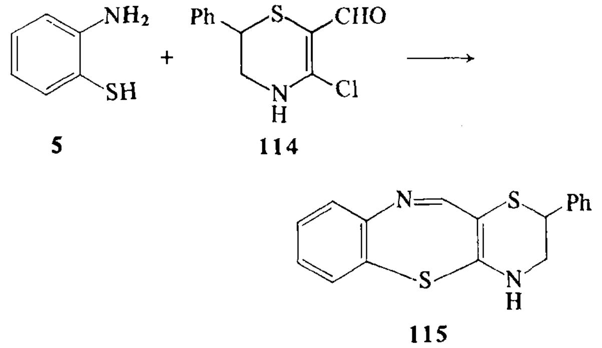
been reported. Derivatives of compound **111** showed strong sedative and muscle relaxant activities.[91]

By condensing 5-acyl-4-chloro-6-methyl-pyrimidines (**112**) with 2-aminothiophenol (**5**) good yields of 1-methyl-11-alkylpyrimido [4,5-*b*] [1,5]benzothiazepines **113** were obtained.[92]



112 **5** **113**

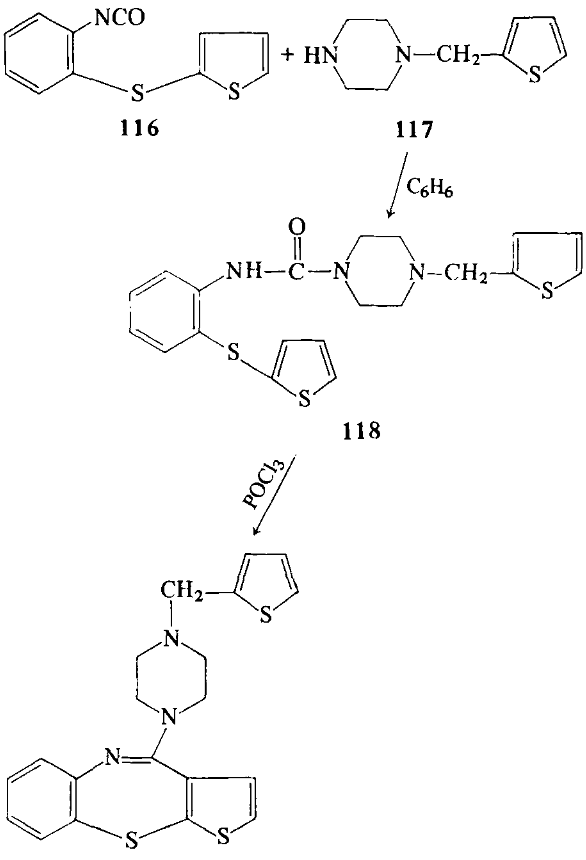
2-Aminothiophenol (**5**) also reacted with 3-chloro-2-formyl-6-phenyl-5,6-dihydro-4H-1,4-thiazine (**114**) in the presence of 2-methylimidazole and gave 72% yield of 2-phenyl-2,3-dihydro-1,4-thiazino[3,2-*b*] [1,5] benzothiazepine (**115**) hydrochloride.[66]



5 **114** **115**

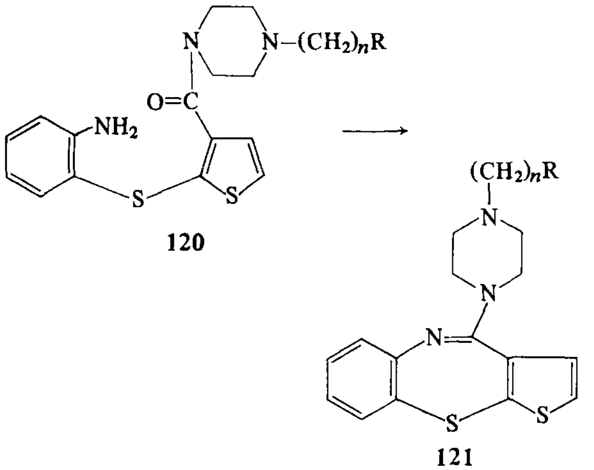
18 THIENOBENZOTHIAZEPINES

Replacement of one benzo group in dibenzo[*b,f*] [1,4]-thiazepine with thiophen ring leading to thienobenzothiazepines has also been accomplished. This was achieved by refluxing a mixture of *o*-(2-thienylthio)-phenyl isocyanate (**116**) for two hours with 1-(2-thenyl)-piperazine (**117**) in benzene resulting in a 90% yield of 4-(2-thenyl)-2′-(2-thienylthio)-1-piperazinecarboxanilide (**118**). Cyclization was achieved by refluxing for 15 hours with phosphorus oxychloride. The thienobenzothiazepine derivative, **119**, was isolated as the hydrated hydrochloride salt.[93] Alternatively, these compounds were obtained by ring closure reactions of the diaryl sulfides, **120**, with mercuric acetate in xylene.[94]



116 **117** **118** **119**

Thienobenzothiazepines of this class were found to be useful agents for the suppression of spontaneous motility and fighting behaviour and for the potentiation of reserpine and narcosis. In tests with mice, the ED_{50} of compound **121** ($n = 2, R$ = 2-pyridyl) was 0.16–0.31 mg/kg for the suppression of spontaneous motility and 10–20 mg/kg for the suppression of fighting behaviour. Ptosis induced by reserpine was increased by 30% at a dose of 0.04–0.08 mg/kg and narcosis by 50% using 0.63 mg/kg of this compound.[93] Many other derivatives which were prepared showed strong sedative,[95] analgesic,[95] antiinflammatory,[95] anticholesterol[95] and antidiabetes activities.[95]



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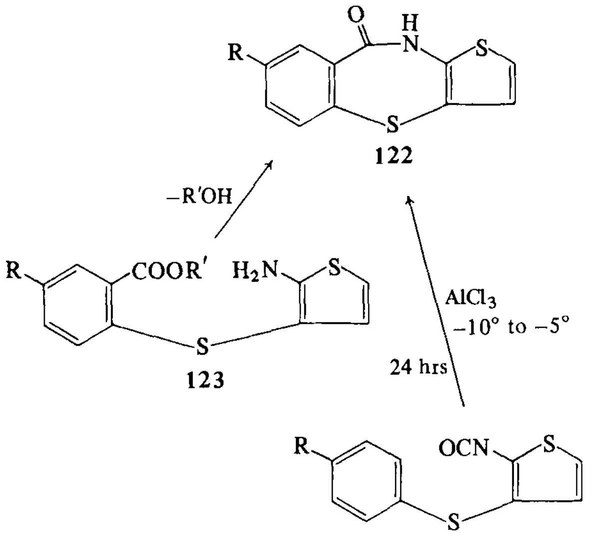
The isomeric thienobenzothiazepines (**122**)[96] were obtained by cyclizing the 2-thienylphenyl sulfides **123**.



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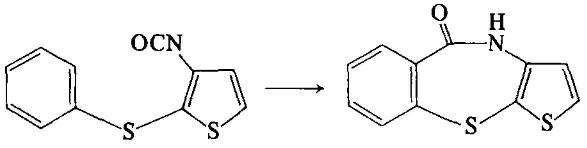
123

Cyclization was also accomplished by intra-molecular rearrangement of a stirred solution of the diaryl isocyanate, **124**, in tetrachloroethane at −10° to −5° for 24 hours in the presence of anhydrous aluminium trichloride.

In tests with laboratory animals, derivatives of these thienobenzothiazepinones (**122**) were found to be useful analgesics,[97,98] sedatives[97,98] and antiinflammatory agents.[97,98]

The third isomeric thienobenzothiazepine was obtained by methods similar to those already described. Thienobenzothiazepinones (**125**) of this class[99] were obtained by cyclization of the diaryl sulfide, **126**, in tetrachloroethane at −10° to −5° in the presence of anhydrous aluminium trichloride during 24 hour period. Derivatives of these thienobenzothiazepines also have sedative,[98] analgesic[98] and antiinflammatory activities.[98]



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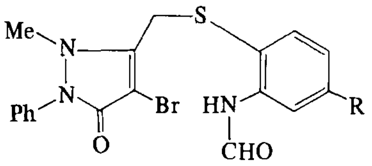
125

19 PYRAZOLOBENZOTHIAZEPINES

Further variation of the dibenzothiazepine ring involves the replacement of one of the benzene rings with pyrazole leading to pyrazolobenzothiazepines (**127**). This was accomplished by Ullmann reaction of 4-bromo-3-(2-formamidophenyl)thiomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (**128**) in a nonpolar solvent such as xylene.[100] In an aprotic polar solvent such as dimethylformamide, the thiazepine ring was not formed. Instead, 3-(3-formylbenzothiazol-2-yl)-2-methyl-1-phenyl-3-pyrazolin-5-one (**132**) was obtained in 62% yield.



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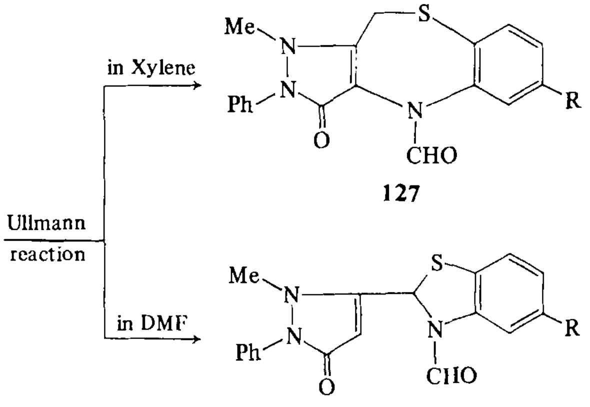

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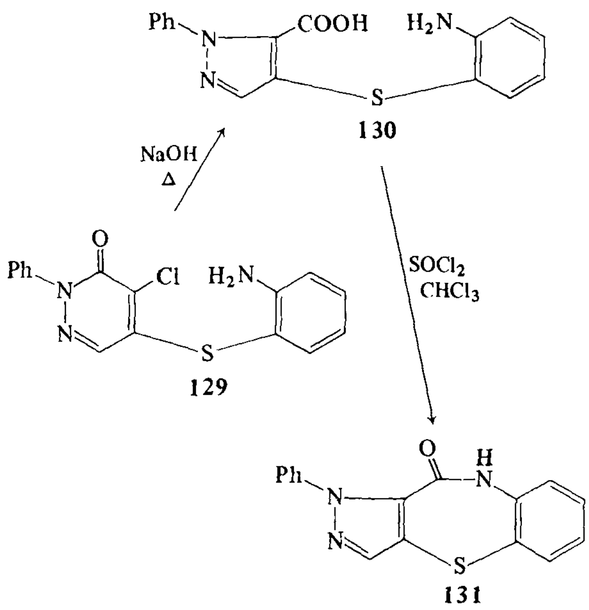
In a method for the synthesis of the isomeric ring system, a suspension of the phenylpyridazinyl sulfide, **129**, was heated for several hours. Ring contration led to the phenylpyrazolyl sulfide **130** which cyclized to the desired isomeric pyrazolobenzothiazepine product **131** on treatment with thionyl chloride in chloroform.[101]



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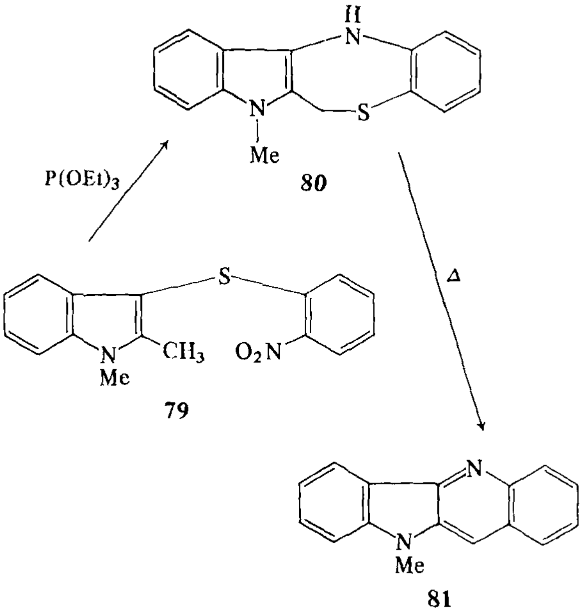
Derivatives of the pyrazolobenzothiazine system (**131**) showed psychotropic activity in laboratory animals.[102]



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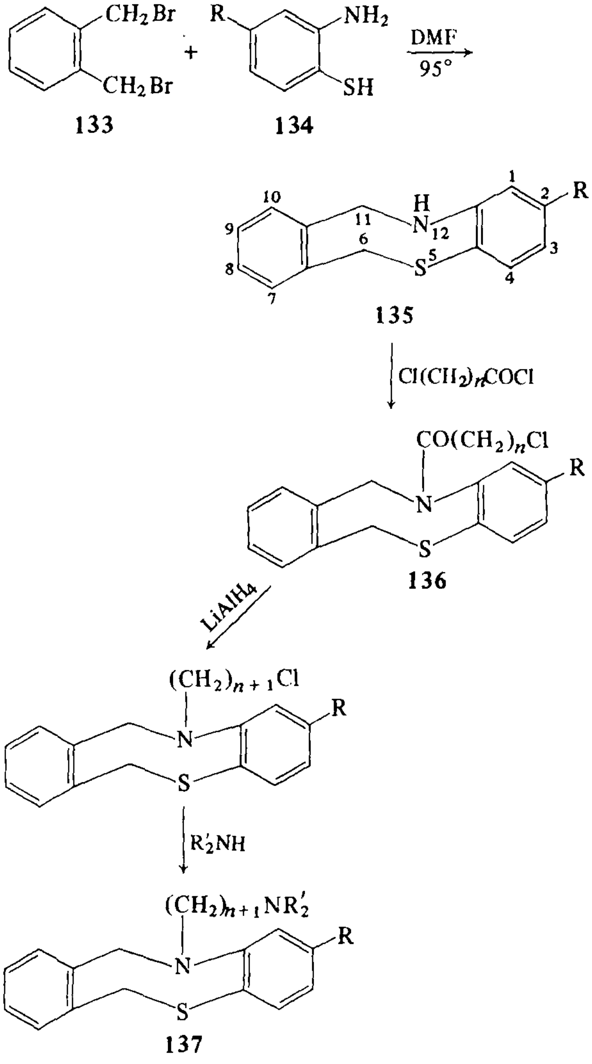
20 INDOLOBENZOTHIAZEPINE

During a study of triethyl phosphite-promoted deoxygenation of indolyl *o*-nitrophenyl sulfides, it was found by Jackson, Johnston and Shannon[60] that the diaryl sulfide **79** was converted to 7-methyl-dihydroindolodihydrobenzothiazepine (**80**) in 34% yield. This product was converted to the indoloquinoline (**81**) on heating above its melting point.

21 DIBENZOTHIAAZOCINES

Further modifications of the central thiazine ring in phenothiazine leading to dibenzothiaazocines have also been made.[103] In the typical reaction, α,α'-dibromo-*o*-xylene (**133**) was condensed with 4-substituted-2-



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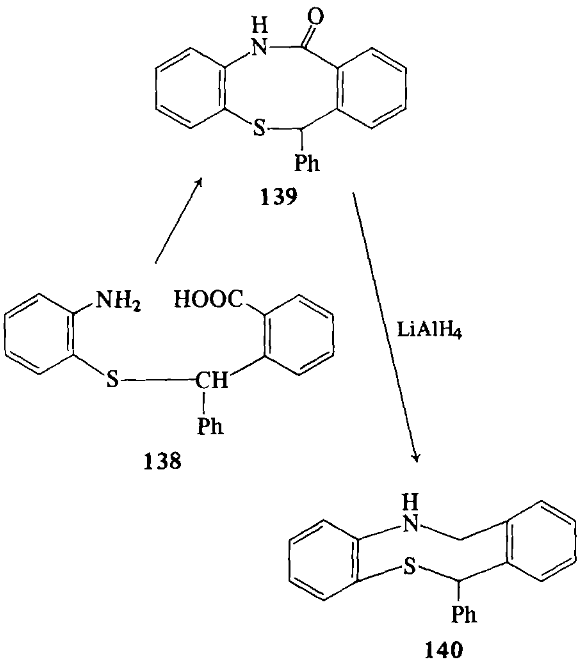
amino-thiophenols (**134**) and gave a 50% yield of 6,11-dihydro-2-substituted-12H-dibenzo[*b*,*f*] [1,4] thiazocine (**135**). Several 2-substituted, N-acyl and N-alkyl derivatives were also prepared.[103–104]

In another method, cyclization of the sulfide **138** with thionyl chloride followed by lithium aluminium hydride reduction afforded 6-phenyl-12H-dibenzo-[*b*,*f*] [1,4] thiazocine (**140**).[105]



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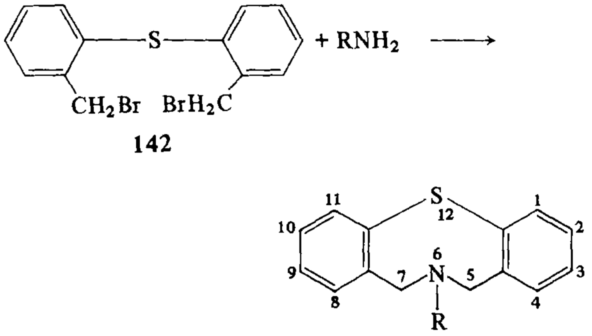
The isomeric dibenzo[*b*,*g*] [1,5] thiazocine (**141**) derivatives have also been prepared. This was accomplished by reacting *o*-bromomethylphenyl sulfide (**142**) with primary amines[106] at 80° in an autoclave for 5 hours. When the reaction mixture was worked-up after the isolation of compound **141**, a sixteen membered ring compound, **142**, was collected as a by-product. The formation ratio depended on the reaction condition.[107–108] Several derivatives of these dibenzothiazocines as well as their 12-dioxides were also reported.[106–115]



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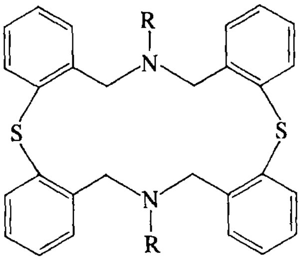

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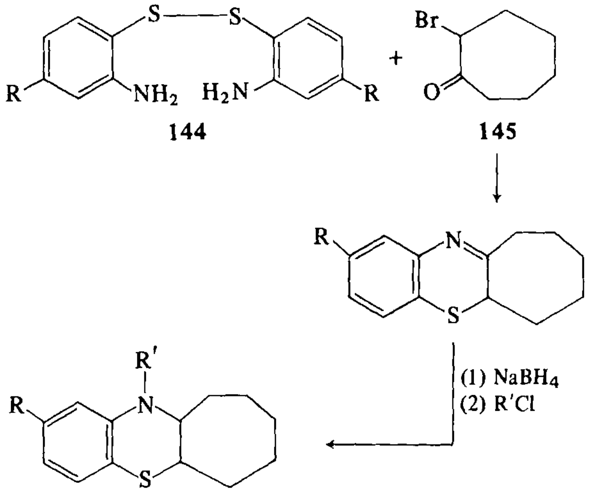
Pharmacological evaluation of these compounds showed that they are useful as antiinflammatory,[106] analgesic,[106] antidepressant[106,109–113] agents as well as parkinsonism inhibitors.[109] The polycyclic thiazocines (**142**) are antiinflammatory,[108] antiedema[108] and psychotropic drugs.[108]

22 BENZOCYCLOHEPTA[*e*] [1,4] THIAZINES

Further variation of the phenothiazine structure was achieved by ring expansion of one of the benzene rings. 2-Substituted-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]-cyclohepta[*e*] [1,4] thiazines (**143**) were obtained by condensing (*o*-aminophenyl)disulfides **144** with 2-bromocycloheptanone (**145**).[116] A number of derivatives were also prepared and their biological properties were studied. These compounds proved to be CNS depressants[116] and weak antihistamines.[116]



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