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The Chemistry and Applications of Angular Phenothiazine Derivatives

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SUMMARY

Since 1883 when Bernthsen, the father of phenothiazine chemistry, synthesized the first compound in this series, several hundreds of derivatives have been made, including angular phenothiazine derivatives of varying structural types.

The angular azaphenothiazines have wide industrial application, typified by their use as dyes and pigments, drugs, sensitizers for photocopying materials, polymerization retardants and particularly as antioxidants in gasoline, grease and other petroleum lubricants.

In this paper, we present a review of the chemistry and uses of angular phenothiazine derivatives.

CHEMISTRY

The chemistry of phenothiazine (**1**) has been of interest to chemists for well over a century. This interest arose from the wide range of its applications. Some phenothiazine derivatives, notably Lauth's Violet (**2**)[1] and Methylene Blue[2] (**3**) were commercially available as dyes even before the discovery of the parent phenothiazine by Bernthsen[3] in 1883.

This interest has been sustained and thousands of derivatives have been reported: a large number of papers and symposia have been concerned[4] with this subject. Several reviews of the chemistry and applications of phenothiazine have also appeared in the literature. Notable among the

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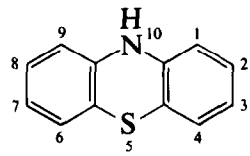

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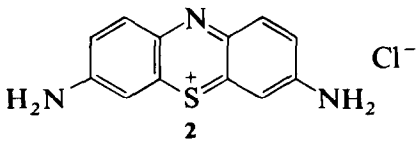

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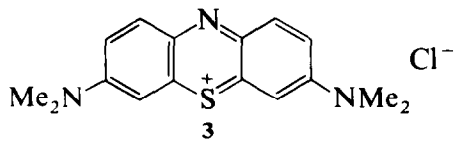

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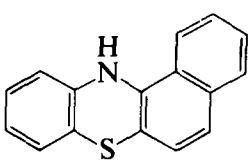
more recent ones are those of Massie[5] and Bodea and Silberg.[6] In these papers, very little reference is made to angular phenothiazines, in spite of their uses as dyes, pigments, antioxidants and their interesting medicinal properties.

Until about the middle of this century most of the reported derivatives of phenothiazine were the side-chain and the 10-alkyl-aminoalkyl derivatives, which were of medicinal interest. In 1945, the first aza-analogue of phenothiazine was reported by Petrow and Rewald.[7] Since then, many other aza-analogues[7-13] and thia-analogues[14-17] have been reported in a search for new and more useful compounds in this series. These new variations have been reviewed in some recent papers.[18,19]

Although the condensed phenothiazines were known even before the dawn of this century, no comprehensive report on the status of work in this area has appeared so far, and we present here the chemistry and commercial uses of angular phenothiazines and their derivatives.

Angular phenothiazines may be defined as phenothiazine derivatives which have non-linear structures. By this definition, they include benzo-[*a*]phenothiazine (**4**), benzo[*b*]phenothiazine (**5**) and the pyridophenothiazines (**6–8**).



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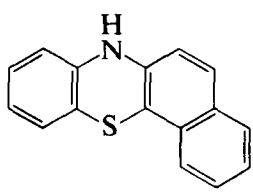

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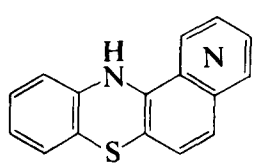

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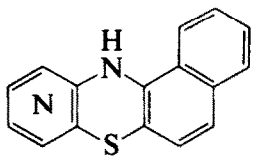

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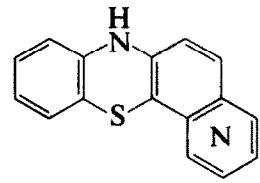

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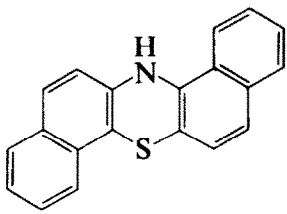
The more complex structures of this type are the dibenzo[*a*,*h*]phenothiazine (**9**), dibenzo[*c*,*h*]phenothiazine (**10**), 14*H*-dibenzo[*a*,*c*]phenothiazine (**11**) and benzo[*a*][1,4]benzothiazine[3,2-*c*]phenothiazine (**12**).



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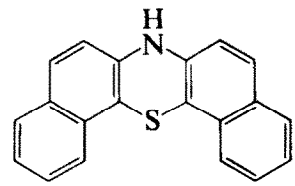

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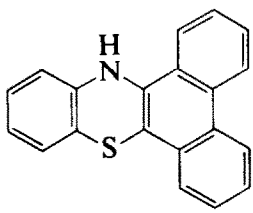

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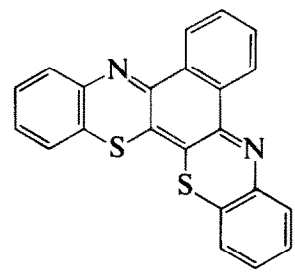

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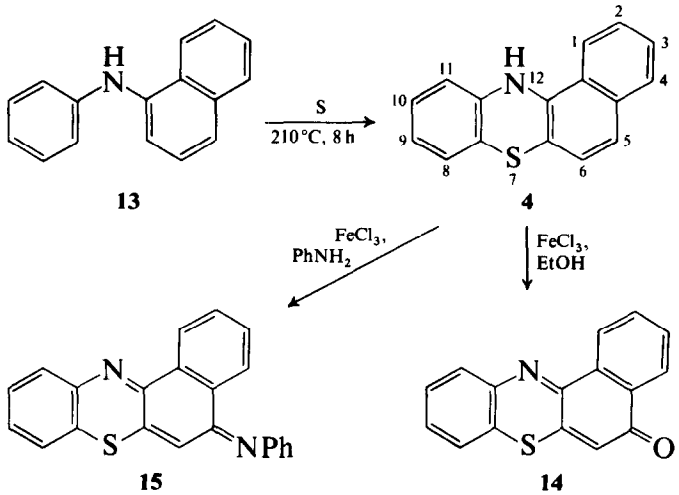
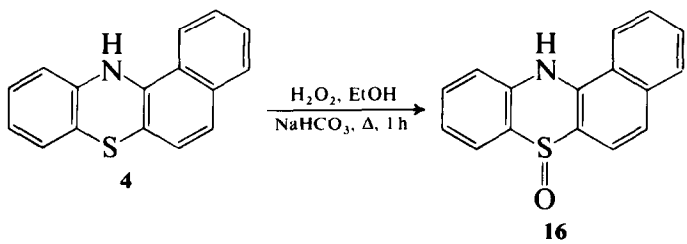
BENZO[*a*]PHENOTHIAZINE RING SYSTEM (4)

The earliest recorded report of an angular phenothiazine was made in 1890 by Kym,[20] who prepared benzo[*a*]phenothiazine (**4**) in 40 % yield by heating 1-anilinonaphthalene (**13**) with sulphur at elevated temperatures. Improved yields and possibly purer products were reported by Shirley,[21,22] who added catalytic amounts of iodine to achieve a 71 % yield. Compound **4**, the parent compound of this ring system, is a yellow solid melting at 134–136 °C. It gives a bluish-green fluorescence in ethanol, benzene and acetic acid solutions.[23]



13 4 15 14

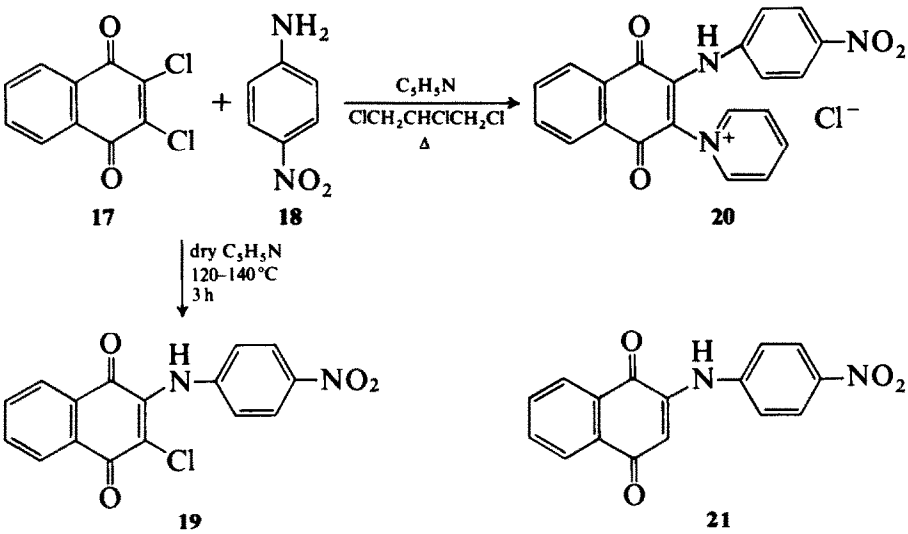
Ferric chloride oxidation gave benzo[*a*]phenothiazin-5-one (**14**) whilst in the presence of aniline the oxidation product is the anil **15**. Alcoholic hydrogen peroxide oxidation converts it to the 7-sulphoxide **16** which decomposes at 194 °C.



4 16

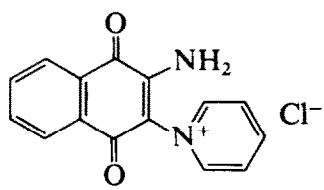
Although the preparation of angular phenothiazines has been known for over a century, the synthesis of this class of phenothiazines from 2,3-dichloro-1,4-naphthoquinone, **17**,[24] is relatively new. The reactivity of compound **17** towards amines was first demonstrated by Plagemann[25] in 1882, who reported its reaction with *p*-nitroaniline (**18**) in pyridine to give 2-chloro-3-(4-nitroanilino)-1,4-naphthoquinone (**19**). This result could not be reproduced by VanAllan and Reynolds[26] who, instead, obtained 2-(4-nitroanilino)-1,4-naphthoquinone-3-pyridinium chloride (**20**).

Treatment of compound **20** with aqueous sodium carbonate was claimed to give 2-(4-nitroanilino)-1,4-naphthoquinone (**21**) in which there is a spurious replacement of chlorine with hydrogen. Compound **21** was earlier obtained by Baltzer[27] by condensing 2-hydroxy-1,4-



17 18 20 19 21

naphthoquinone with **17**. The controversy was, however, settled by Agarwal and Schafer[28] who isolated Plagemann's product **19** in 3% yield together with product **22** obtained in 23% yield as the major product. They could not isolate VanAllan's compound **21** although an excellent yield of compound **20** (77%) was obtained in 1,2,3-trichloropropane and pyridine as previously reported.[26]



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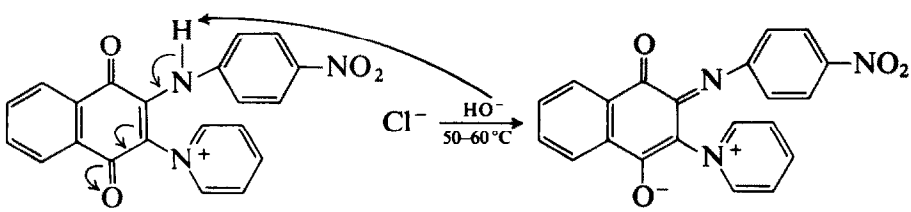
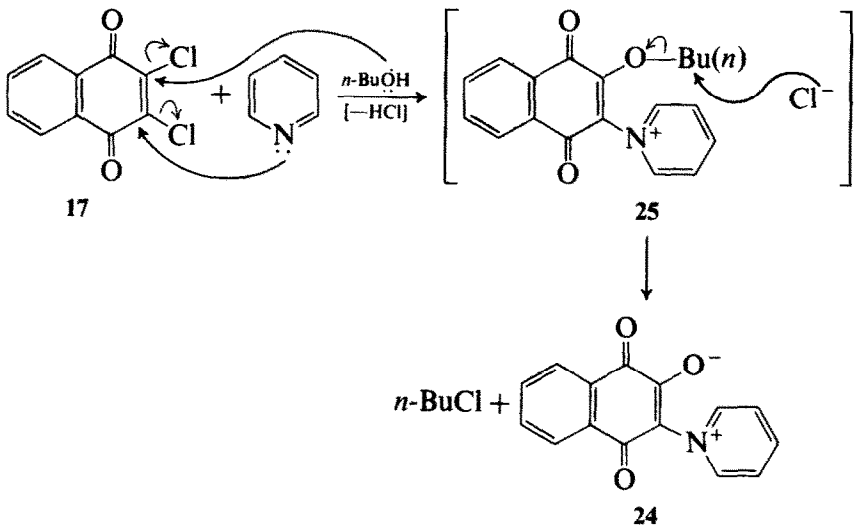
Reaction of compound **20** with alkalis was reinvestigated by Agarwal,[28] who proved that the structure of the orange-red compound produced in 94% yield was 1-oxo-2-(4-nitrophenylimino)-3-pyridinium-4-naphthoxide (**23**).



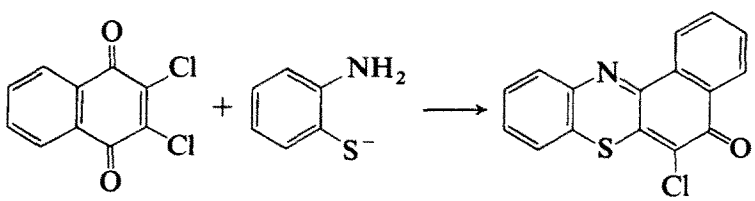
20 **23**

The reaction of **17** with pyridine in butanol gave 1,4-dioxo-3-pyridinium-2-naphthoxide (**24**), a useful intermediate for the synthesis of benzo[*a*]phenothiazin-5-ones. Product **24** is identical with an authentic sample previously prepared by Ullman and Ettisch.[29] This compound is probably formed by the nucleophilic displacement of both chlorine atoms by the nucleophiles, butoxide ion and pyridine. This would lead to the intermediate compound **25**. Loss of butyl chloride through hydrolysis would give product **24**. This type of elimination had earlier been reported for 1,4-diazaphenanthrenes.[25]



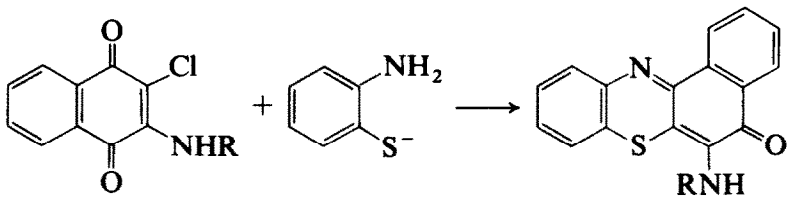
17 25 24

When 1:1 molar ratios of 2,3-dichloro-1,4-naphthoquinone were refluxed with the zinc salt of *o*-aminothiophenol (**26**) or any other *o*-aminothiophenoxide salt, 6-chloro-5*H*-benzo[*a*]phenothiazin-5-one (**27**) was obtained in 84% yield.



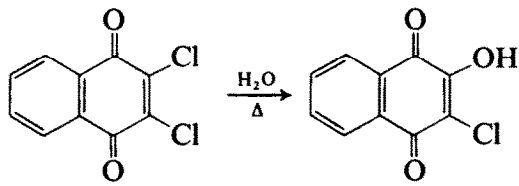
17 27

There was however no reaction[30] when compound **24** was treated with the zinc salt of *o*-aminothiophenol. With 2-chloro-3-amino-1,4-naphthoquinones (**28**), the corresponding angular phenothiazines **29** were obtained in varying yields[31–35]



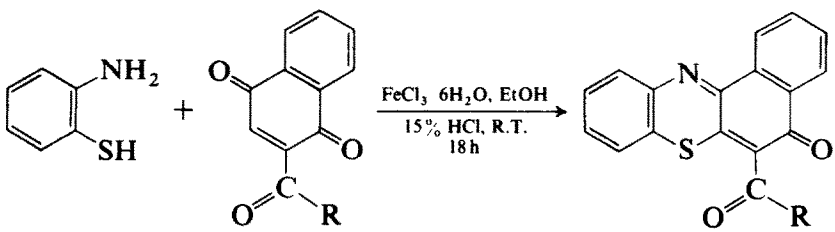
28 **29**

In all these reactions, anhydrous conditions were maintained because of the tendency of compound **17** to hydrolyse to give the less reactive 2-hydroxy derivative **30**.



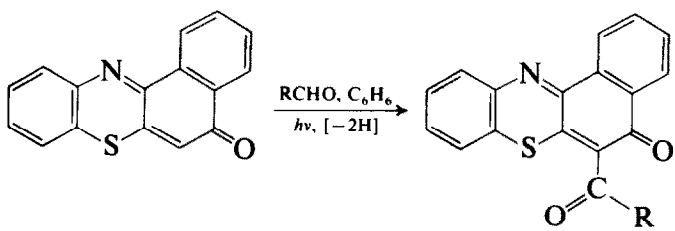
17 **30**

Oxidative condensation[36] of 2-acyl-1,4-naphthoquinones (**31**) with *o*-aminothiophenol in the presence of ferric chloride gave 6-acyl-5*H*-benzo[*a*]phenothiazin-5-ones (**32**) in yields varying from 10 to 15%.



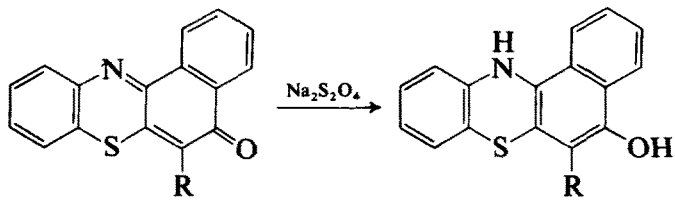
26 **31** **32**

Light-induced reaction of 5*H*-benzo[*a*]phenothiazin-5-one (**14**) with aldehydes led to the same products, **32**, in much improved yields of 63 to 90%.[36]



14 **32**

Reduction of these quinoid compounds with sodium hydrosulphite ($Na_2S_2O_4$) produced the corresponding phenols (**33**).[33-35]



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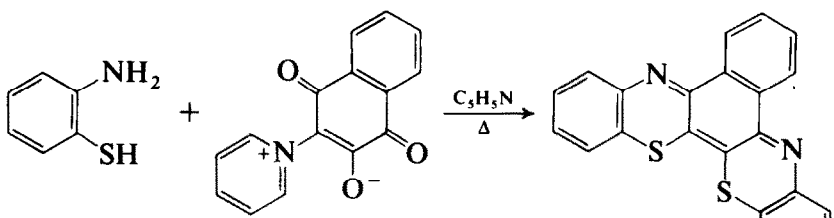
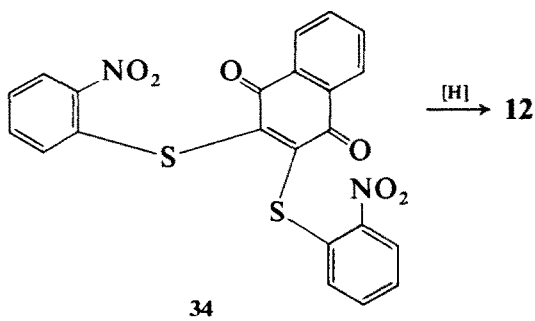
BENZO[*a*][1,4]BENZOTHIAZINO[3,2-*c*]PHENOTHIAZINE RING SYSTEM (**12**)

Benzo[*a*][1,4]benzothiazino[3,2-*c*]phenothiazine (**12**), a triangular phenothiazine, was prepared[26] in high yields by the action of *o*-aminothiophenol (**26**) on 1,4-dioxo-3-pyridinium-2-naphthoxide (**24**) in dried pyridine. Fries and Ochwat[37] had earlier claimed that the same product



26 **24** **12**

could be obtained by the reduction of 2,3-bis(*o*-nitrophenylthio)-1,4-naphthoquinone (**34**), but the melting point of their product (> 350 °C) is different from that reported by VanAllan and Reynolds (m.p. 291 °C).



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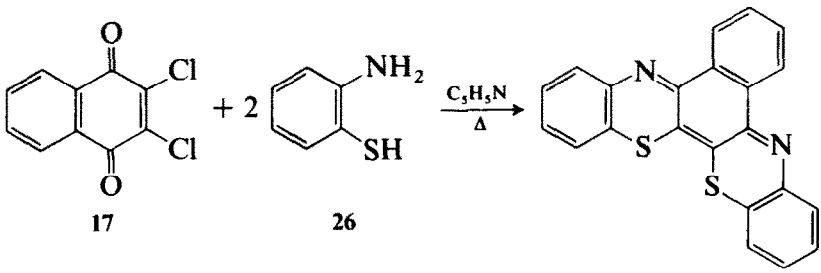
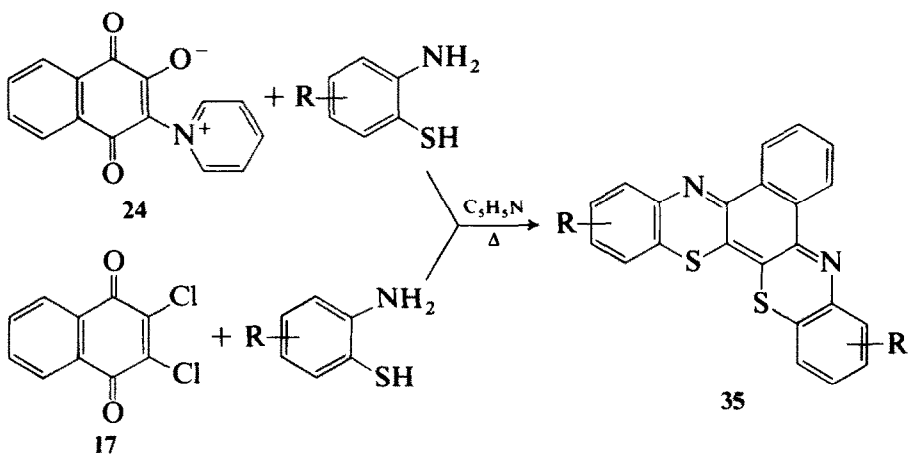
This controversy was eventually resolved by Agarwal and Mital,[30] who obtained a product, m.p. 291 °C, identical with VanAllan's compound when he reacted 2,3-dichloro-1,4-naphthoquinone (**17**) with *o*-amino-thiophenol in dry pyridine. Using substituted *o*-aminophenols, several



17 **26** **12**

derivatives of benzo[*a*][1,4]benzothiazino[3,2-*c*]phenothiazine (**35**) were obtained by reactions with compound **17** or **24** in dry pyridine.[30]

It may be noted from these reactions that angular phenothiazines of type **27** are obtained if the reactions of **17** with amino thiophenols are carried out in alkaline media, but in the absence of a base the triangular phenothiazines **35** result.



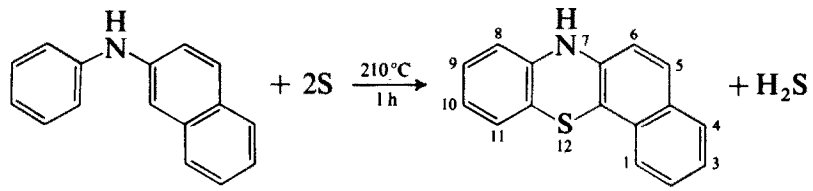
24 **35** **17**

BENZO[*c*]PHENOTHIAZINE RING SYSTEM (**5**)

In conjunction with their studies on benzo[*a*]phenothiazines, Kehrmann and Christopoulos[23] investigated the chemistry of isomeric benzo-[*c*]phenothiazines. The parent compound **5** was obtained in 80% yield by

thiation of 2-anilinonaphthalene at 210 °C for 1 h. With the addition of catalytic amounts of iodine, Shirley[22] obtained the same compound but in 66% yield.

Compound **5** is a yellow solid melting at 178 °C and shows green fluorescence in benzene or ethanol.



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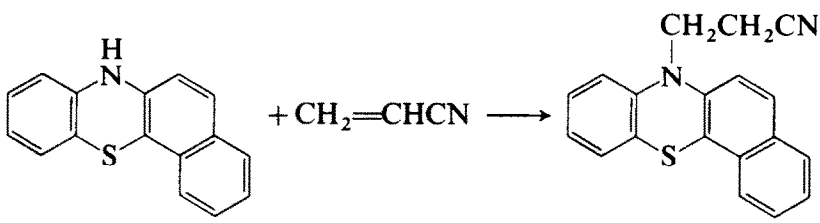
Benzo[*c*]phenothiazine reacts with acrylonitrile to give a yellow solid, melting at 215 °C and identified as benzo[*c*]phenothiazine-7-propionitrile (**36**). Compound **36** is used commercially[38] as an antioxidant for gasoline and petroleum lubricants.

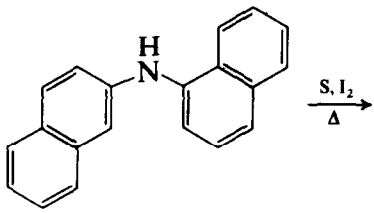


5 **36**

DIBENZO[*a*,*h*]PHENOTHIAZINE RING SYSTEM (**9**)

In addition to the monobenzophenothiazines, the dibenzophenothiazines have also been reported. The parent dibenzo[*a*,*h*]phenothiazine (**9**) was obtained in 55% yield by the pyrolysis of 2-naphthyl-1-naphthylamine (**37**) and sulphur in the presence of a small quantity of iodine.[39]

Compound **9** is a solid melting at 194–197 °C. 14-Alkylations (compounds **38**) were achieved by treatment with *n*-butyl lithium followed by the action of the alkyl tosylates.[22] Treatment of compound **9** with acetic anhydride and anhydrous zinc chloride at room temperature for over 24 h gave 14-acetyl-14*H*-dibenzo[*a*,*h*]-phenothiazine (**39**) which can



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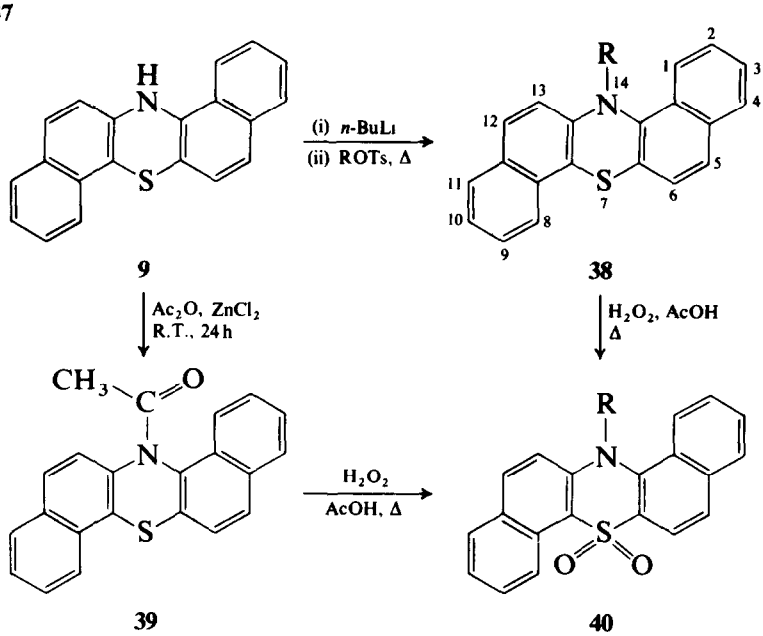
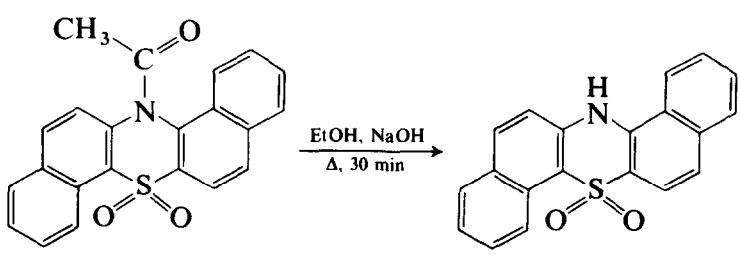


9 38

39 40

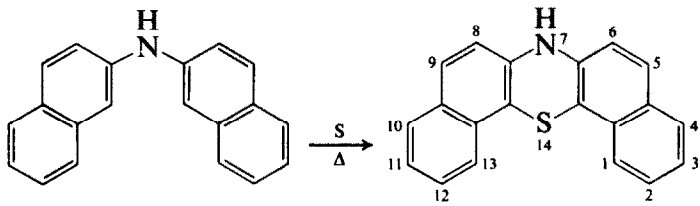
be transformed to the 7,7-dioxide (**40**, R = CH_3CO) by peroxide oxidation in acetic acid. Deacetylation of compound **40** was achieved by refluxing an ethanolic suspension with aqueous sodium hydroxide solution for half an hour. 14*H*-Dibenzo[*a*,*h*]-phenothiazine 7,7-dioxide (**41**) was obtained as a yellow solid,[22] m.p. 407 °C, in 83% yield.



40, R = CH_3CO 41

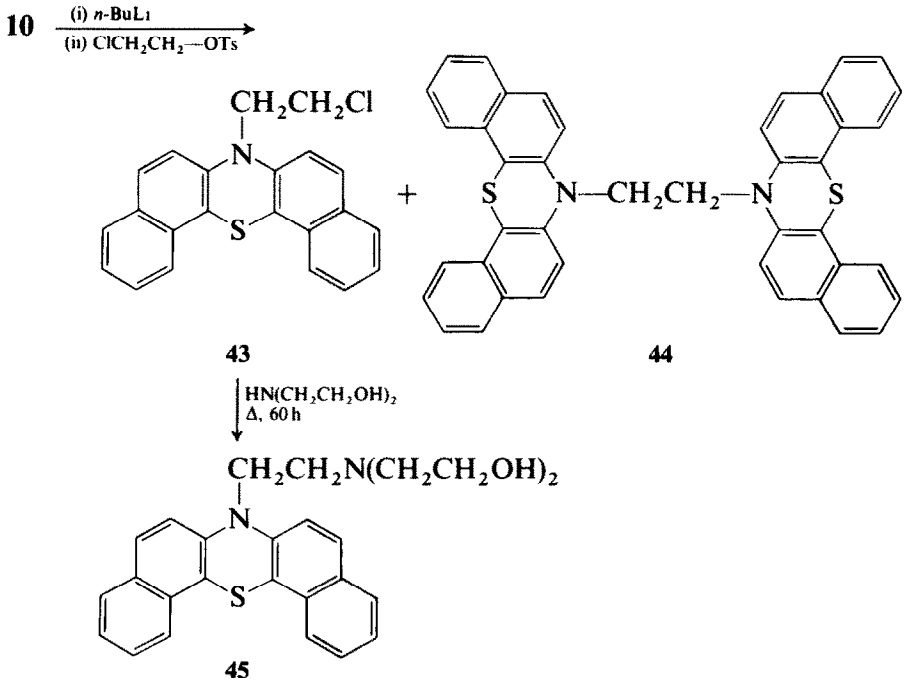
DIBENZO[*c*,*h*]PHENOTHIAZINE RING SYSTEM (**10**)

Isomeric dibenzophenothiazines of type **10** have been prepared in addition to compound **9**. Dibenzo[*c*,*h*]phenothiazine (**10**), the parent compound, was prepared by the pyrolytic reaction of 2,2′-dinaphthylamine (**42**) with elemental sulphur.[22,40]



42 **10**

Shirley reported a yield of 80% and the product decomposed at 228–230°C. Treatment with *n*-butyllithium followed by the action of alkyl tosylates gave the 7-alkyl derivatives. Compound **10** reacts in this manner with *n*-butyllithium and 2-chloroethyltoluene *p*-sulphonate to give 7-(2-chloroethyl)-7*H*-dibenzo[*c*,*h*]phenothiazine (**43**) (25% yield)



43 **44**

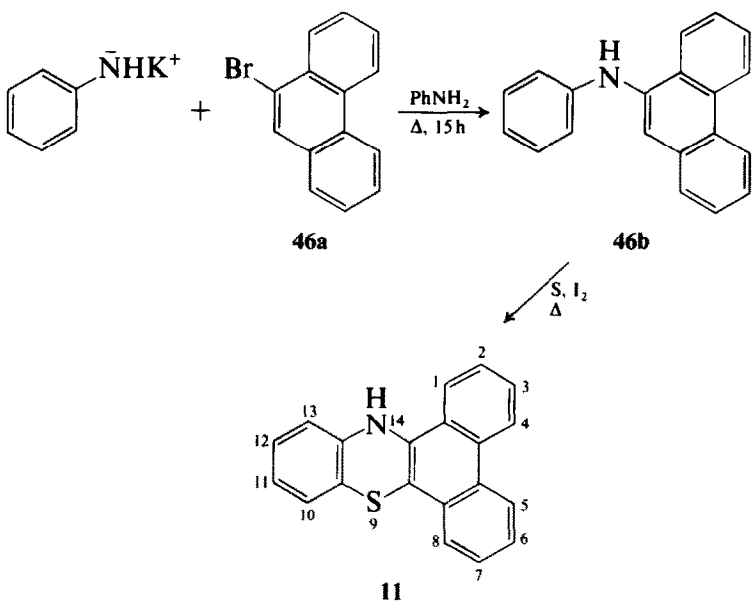
45

and a small quantity of a red solid (m.p. 240–240·5 °C) which was identified as 1,2-bis(7*H*-dibenzo[*c*,*h*]phenothiazin-7-yl)ethane (**44**).

Heating compound **43** and diethanolamine at 135–140 °C for 60 h gave 7-[2-bis(2-hydroxyethyl)aminoethyl]-7*H*-dibenzo[*c*,*h*]phenothiazine (**45**) which can be converted to the bis(2-chloroethyl)amino derivative in 67% yield by reaction with $POCl_3$.[22]

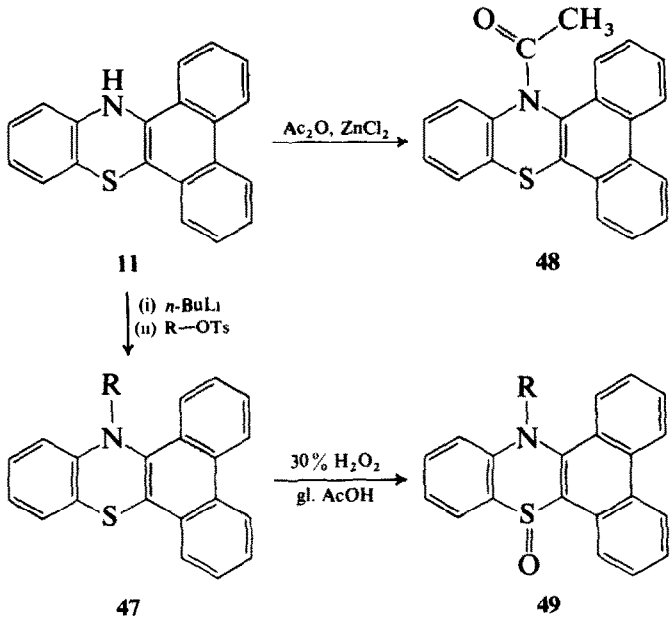
14*H*-DIBENZO[*a*,*c*]PHENOTHIAZINE RING SYSTEM (11)

The third isomeric dibenzophenothiazine, **11**, was prepared by converting 9-bromophenanthrene (**46a**) to 9-anilinophenanthrene (**46b**) by reaction with potassium anilide followed by iodine-catalyzed reaction of the resulting diarylamine with sulphur at 155–205 °C. A yield[22] of only 16% was realized because of the strong reaction condition.



11

14*H*-Dibenzo[*a*,*c*]phenothiazine (**11**) is a yellow solid melting at 160–164 °C. It was successfully acetylated in 65% yield by the action of acetic anhydride and zinc chloride. 14-Alkyl derivatives (**47**) were obtained by the action of *n*-butyllithium followed by refluxing with alkyl *p*-toluene sulphonate.



Oxidation with 30% hydrogen peroxide in glacial acetic acid converted them to their 9-sulphoxides (**49**) rather than sulphones.

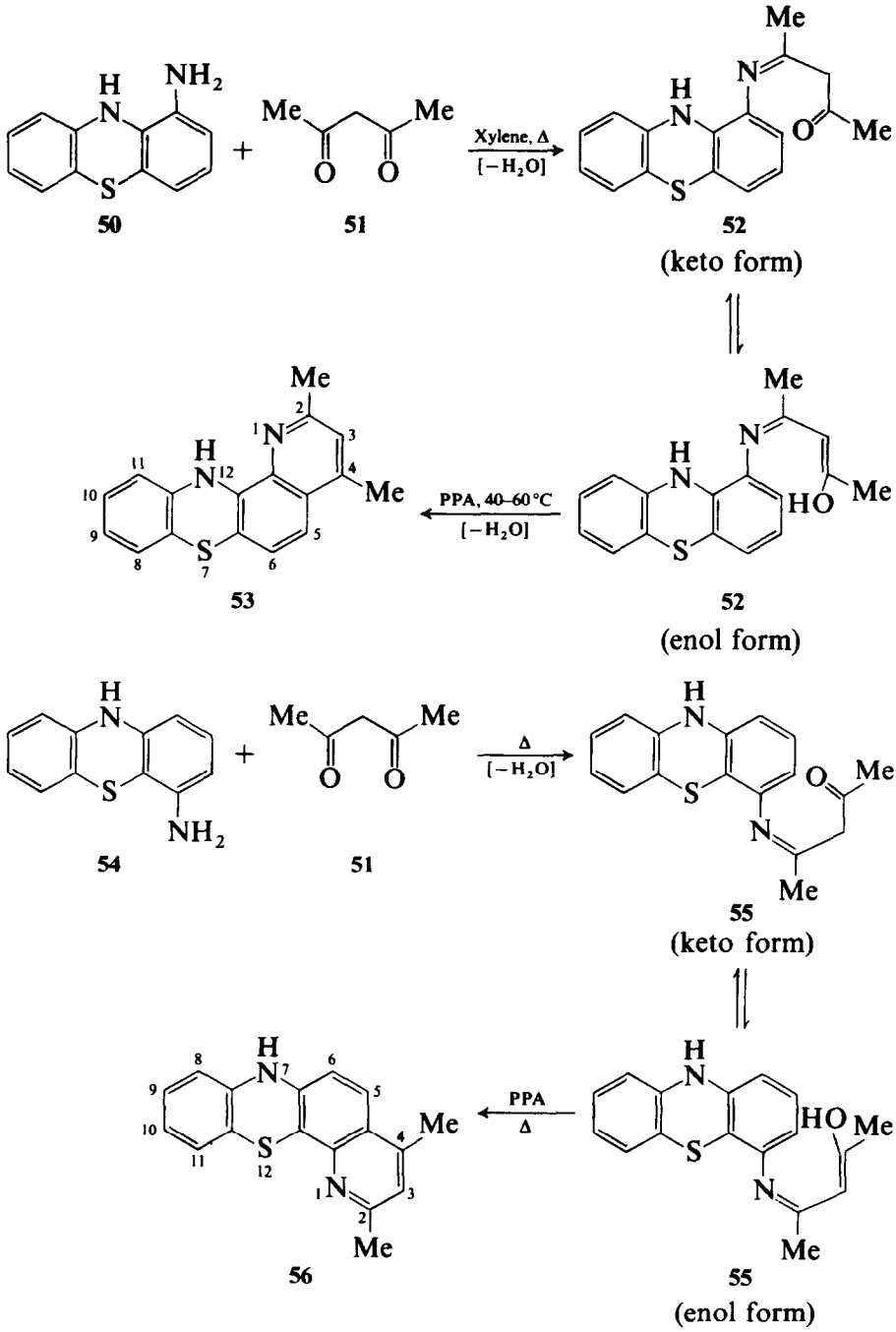
PYRIDO[2,3-*a*]PHENOTHIAZINE RING SYSTEM (53)

The compounds described above have all been carbocyclic benzophenothiazines in which benzene rings are fused with the phenothiazine ring system. The aza-analogues of these benzophenothiazines have also been studied.

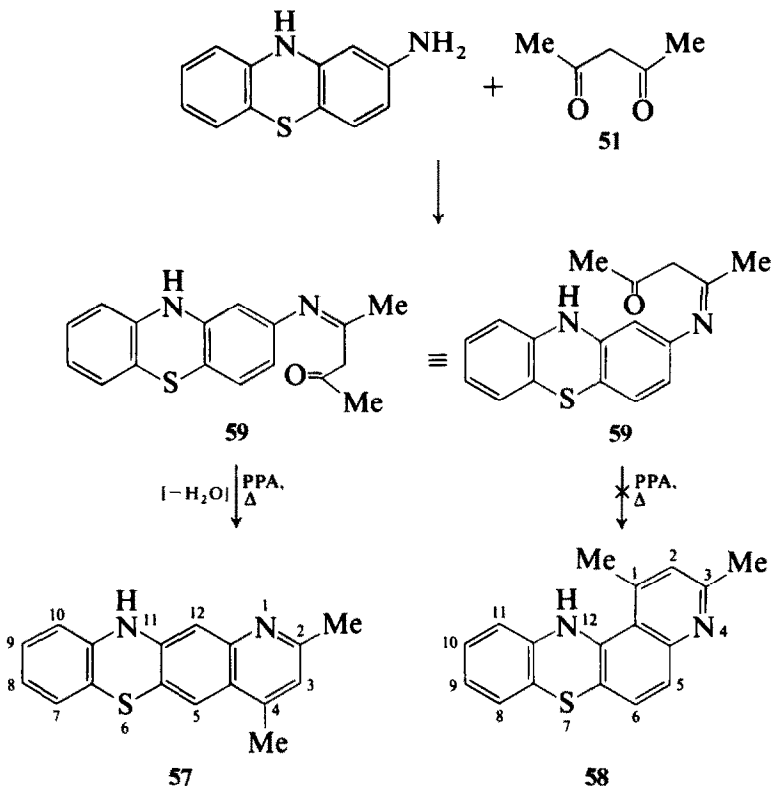
1-Aminophenothiazine (**50**) reacts with penta-2,4-dione (**51**) in xylene to give compound (**52**) which on cyclization with polyphosphoric acid (PPA) at 40–60 °C gave 2,4-dimethylpyrido[2,3-*a*]phenothiazine (**53**) in 64% yield.[41]

PYRIDO[3,2-*c*]PHENOTHIAZINE RING SYSTEM (56)

The isomeric pyrido[3,2-**c**]phenothiazine ring system has also been reported. It was synthesized by the reaction of 4-aminophenothiazine (**54**) with penta-2,4-dione (**51**) in xylene followed by cyclization of the anil **55**


Xylene, Δ
[−H2O]
PPA, 40–60 °C
[−H2O]
Δ
[−H2O]
PPA
Δ
50
51
52
(keto form)
52
(enol form)
53
54
55
(keto form)
55
(enol form)
56

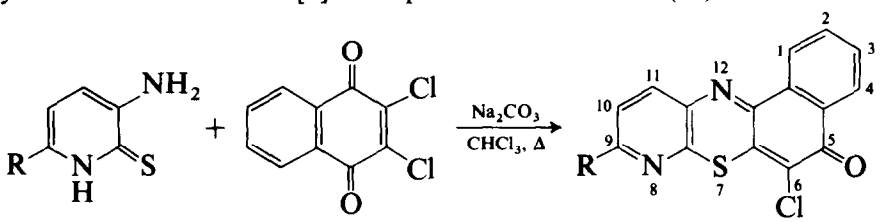
in polyphosphoric acid. 2,4-Dimethylpyrido[3,2-*c*]phenothiazine (**56**) was obtained[41] in 65% yield in this way. If the reactions were repeated with 2-aminophenothiazine, two products, **57** and **58**, could be expected depending on whether it is the C-3 or C-1 of the phenothiazine ring that is attacked during the cyclization of the anil **59**. Only one product was isolated: it was 2,4-dimethyl-1*H*-pyrido[2,3-*b*]phenothiazine (**57**)[41] and not 1,3-dimethyl-12*H*-pyrido[3,2-*a*]phenothiazine (**58**). Compound **57**, obtained in 60% yield, is a derivative of a linear phenothiazine system.



It may be pointed out at this juncture that while several naturally occurring derivatives[42–53] of phenoxazine and the oxygen analogue of the angular azaphenothiazine **6** are known, no phenothiazine derivative is so far known to occur in nature, either in plants or animals. Nevertheless, the search for new phenothiazines has continued unabated because of their numerous applications compared with their azaphenoxazine analogues.

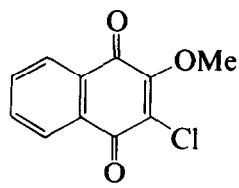
BENZO[*a*]-8-AZAPHENOTHIAZINE RING SYSTEM (61)

Whilst the above are aza-analogues of angular phenothiazine containing the nitrogen atom in ring A, analogues in which the ring nitrogen is in ring D have recently been reported. 3-Aminopyridine-2[1*H*]-thiones (**60**)[54] react with 2,3-dichloro-1,4-naphthoquinone (**17**) in chloroform or benzene in the presence of anhydrous sodium carbonate to afford good yields of 6-chlorobenzo[*a*]-8-azaphenothiazin-5-ones (**61**).[55]



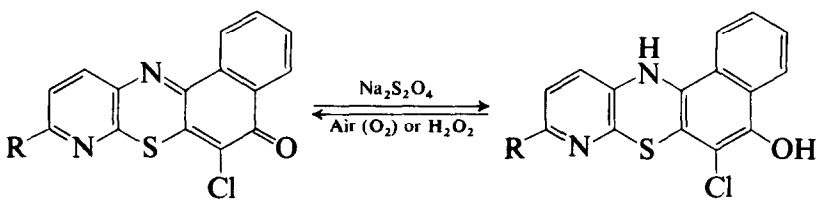
60 **17** **61**

If these reactions were carried out in non-aqueous hydroxylic solvents such as ethanol and methanol, a second product identified as 2-chloro-3-alkoxy-1,4-naphthoquinone was isolated. Using methanol as a solvent, 2-chloro-3-methoxy-1,4-naphthoquinone (**62**) was isolated together with the expected angular azaphenothiazines **61**.



62

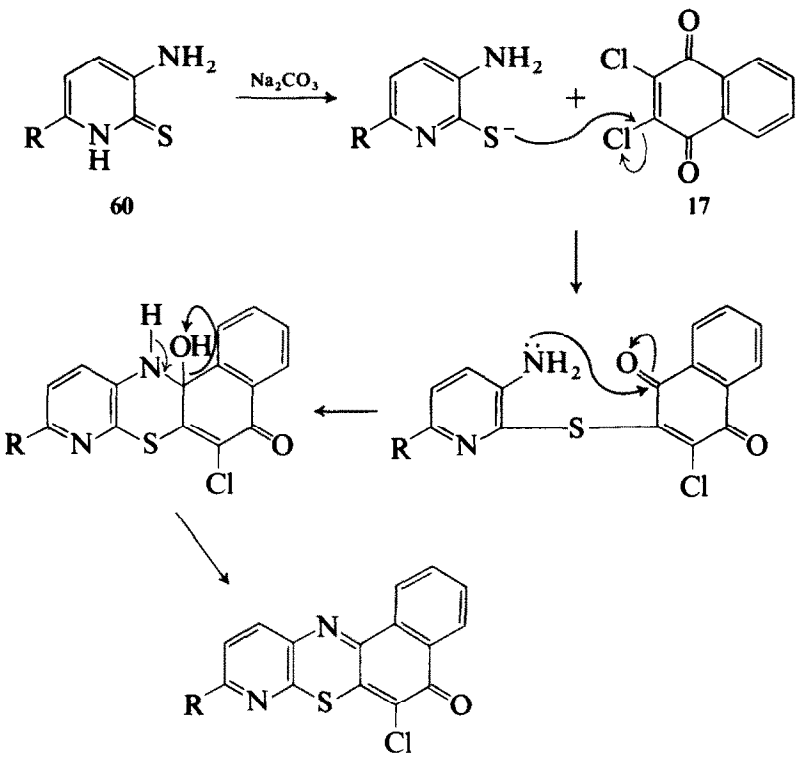
Reduction of these angular azaphenothiazines **61** with sodium hydrosulphite ($Na_2S_2O_4$) gave the angular azaphenothiazin-5-ols (**63**). These reduced compounds were unstable to air and readily revert to the oxidized form **61** on exposure to oxygen of the air. On shaking with hydrogen peroxide the azaphenothiazinols **63** more quickly revert to **61**.



61 **63**

The instability of these angular azaphenothiazin-5-ols **63** in atmospheric oxygen is in agreement with an earlier observation on this class of compounds.[56]

These compounds are probably formed through the mechanistic pathway shown in Scheme 1.



61

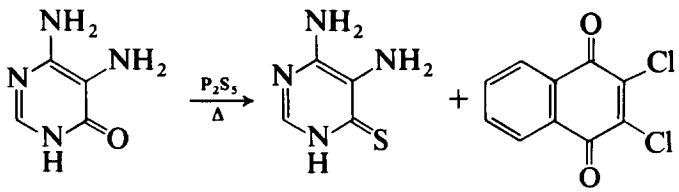
Scheme 1

The ease of formation of these compounds from relatively cheap materials and their interesting colours which range from brown through red to purple suggest their possible use as dyes and pigments, particularly as vat dyes.

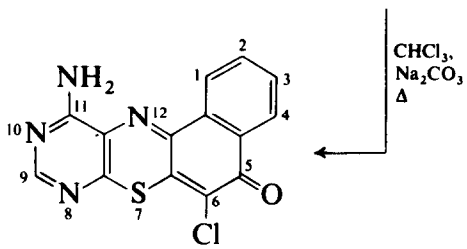
BENZO[*a*]-8,10-DIAZAPHENOTHIAZINE RING SYSTEM (66)

As a further variation of the angular azaphenothiazines, derivatives of the benzo[*a*]-8,10-diazaphenothiazine ring system have been reported

recently.[55] This class of angular diazaphenothiazines was obtained from 4,5-diaminopyrimidin-6[1*H*]-one (**64**). Compound **64** was converted to 4,5-diaminopyrimidine-6[1*H*]-thione (**65**) by the action of P_2S_5. Condensation of the pyrimidinethione with 2,3-dichloro-1,4-naphthoquinone (**17**) in anhydrous alkaline solutions gave 98% yield of 11-amino-6-chlorobenzo[*a*]-8,10-diazaphenothiazin-5-one (**66**).

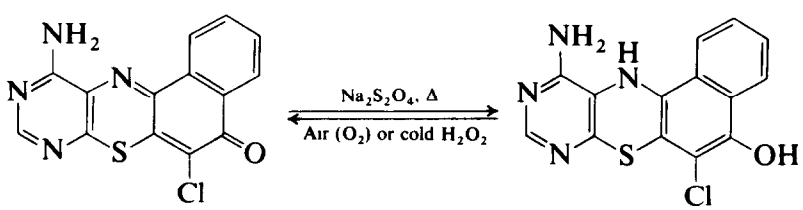


64 **65** **17**



66

Reduction with sodium hydrosulphite gave the corresponding angular diazaphenothiazin-5-ol (**67**), which could not be isolated in the pure form as it is readily oxidized by atmospheric oxygen to the more stable quinoid structure **66**.

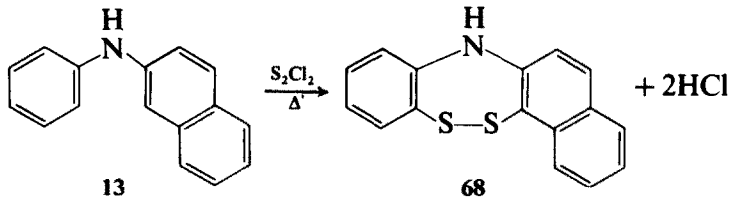


66 **67**

Cold dilute hydrogen peroxide accelerates the oxidation of **67** to the quinone form **66** by shaking the suspension of compound **67** in a suitable solvent with hydrogen peroxide solution.

BENZO[*c*]NAPHTHO[2,1-*f*]-5*H*-1,2,5-DITHIAZEPINE RING SYSTEM (68)

Related to these angular phenothiazines is benzo[*c*]naphtho[2,1-*f*]-5*H*-1,2,5-dithiazepine (**68**) prepared[57] by the action of sulphuryl chloride on 2-anilinonaphthalene (**13**).

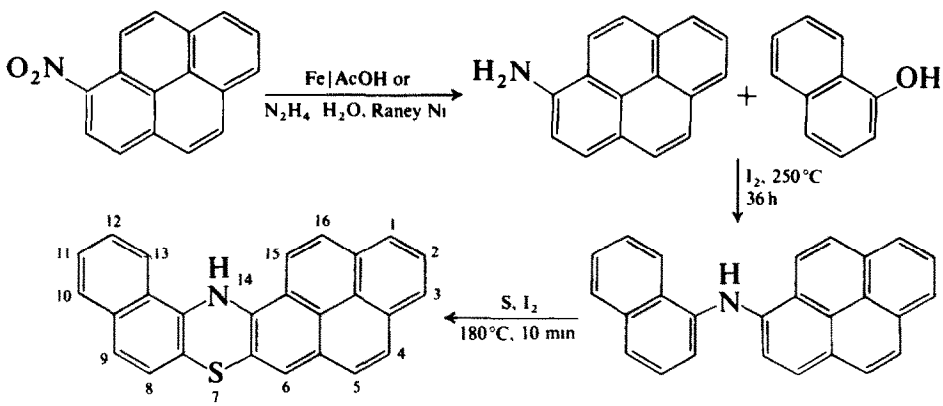


13 68

MISCELLANEOUS ANGULAR PHENOTHIAZINES

14*H*-Benzo[*j*]phenaleno[1,9-*ab*]phenothiazine ring system (69)

In addition to the simple benzophenothiazines thus described, more complex polycyclic angular phenothiazines have been reported. Buu-Hoi[58] prepared 14*H*-benzo[*j*]phenaleno[1,9-*ab*]phenothiazine (**69**) according to Scheme 2.



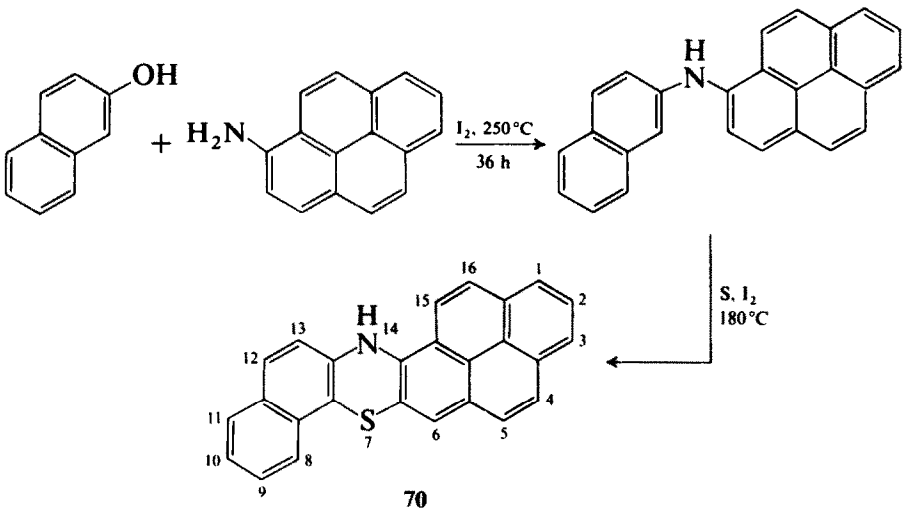
69

Scheme 2

Product **69**, a polycyclic phenothiazine derivative, is a deep yellow solid, m.p. 270°C. It gave an indigo-blue colour in sulphuric acid.

14*H*-Benzo[*h*]phenaleno[1,9-*ab*]phenothiazine ring system (70)

Isomeric with compound **69** is 14*H*-benzo[*h*]phenaleno[1,9-*ab*]phenothiazine (**70**) which is prepared[58] from 1-aminopyrene and 2-naphthol as follows:



70

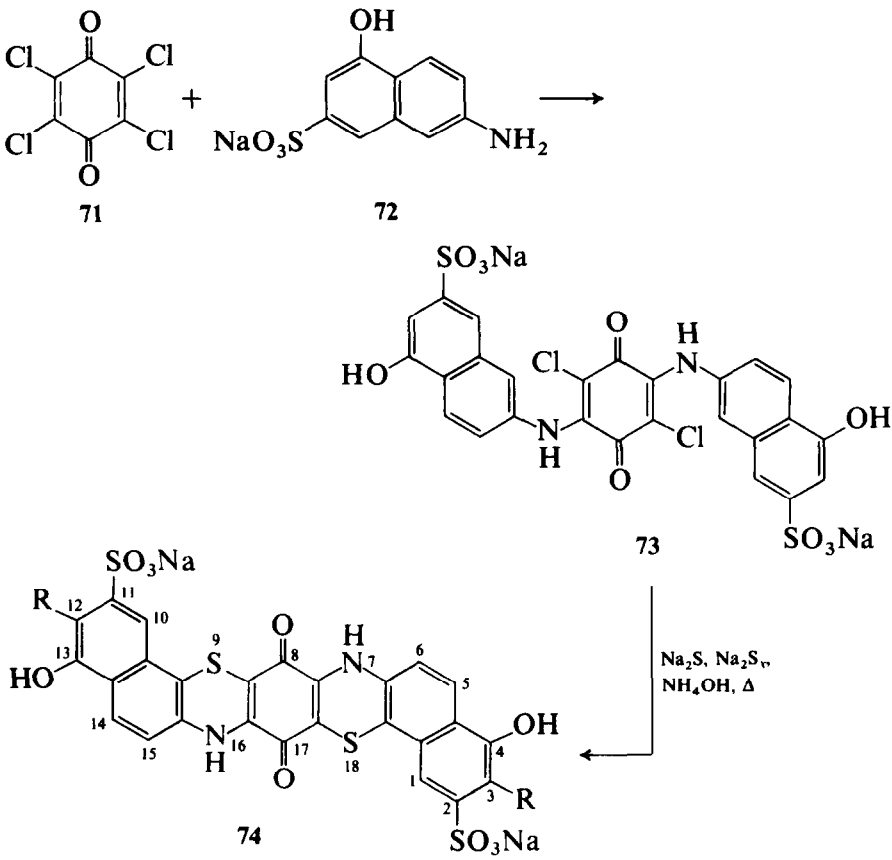
Dibenzo[*c*,*n*]triphenodithiazine ring system (74)

Interesting dyes having angular dithiazine structures have been prepared. Chloranil **71**, reacts with 6-amino-3-sulpho-1-naphthol (**72**) in ethanol–acetone solution in the presence of sodium acetate to give the diacylamine precursor **73**, a light brown crystalline solid. Heating compound **73** with sodium sulphide fused with sodium polysulphide (Na_2S_x), or preferably refluxing with Na_2S_x in dilute ammonium hydroxide for several hours, gave disodium 2,11-disulpho-4,13-dihydroxydibenzo[*c*,*n*]triphenodithiazin-8,17-dione (**74**, R = H) in good yields.[59]

Product **74**, R = H, is a dark green crystalline material. It is a good vat dye for cotton but is not good for wool. Cotton dyed with compound **74**, R = H, and then treated with a diazotized aromatic amine gave reddish-brown to Bordeaux coloured materials due to 2,12-diazo-coupling with the diazotized amines to form compounds **74**, R = N=NAr.

Dibenzo[*c*,*n*]triphenodithiazine of type **75** is obtained by converting

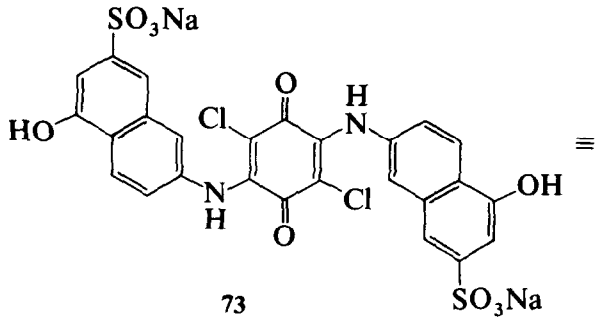
the diacylamine **73** to the disodium salt of 2,11-sulpho-4,13-dihydroxy-8,17-dichlorodibenzo[*c*,*n*]triphenodioxazine (**76**). Treatment of compound **76** with aqueous sodium sulphide gave the sulphur analogue, disodium 2,11-sulpho-4,13-dihydroxy-8,17-dichlorodibenzo[*c*,*n*]triphenodithiazine (**75**).



Product **75** is a good green dye for cotton.[59]

Phenaleno[1,9-*ab*]pyreno[1′,2′:5,6][1,4]thiazino[3,2-*i*]phenothiazine ring system (78)

Polycyclic dyes which are good for dyeing cotton have been commercially produced by ICI by heating 1-aminopyrene and hydroquinone at a high temperature. The resulting diamine, **77**, was heated with sulphur in



73

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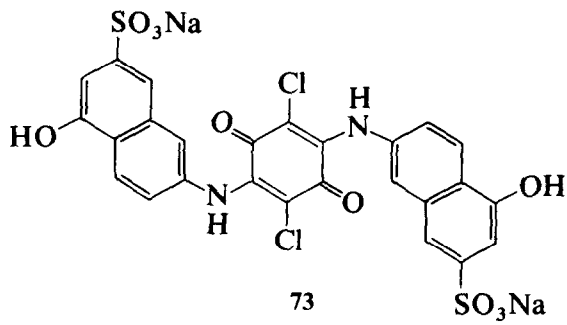

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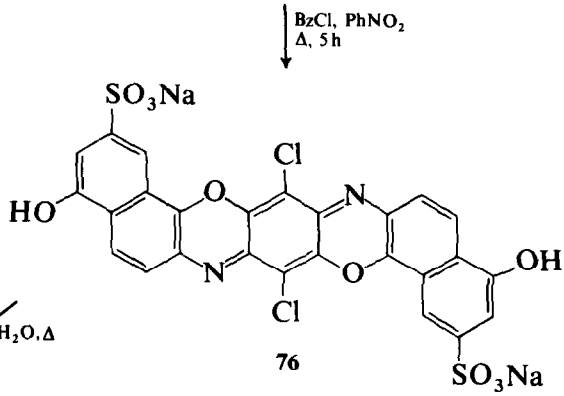
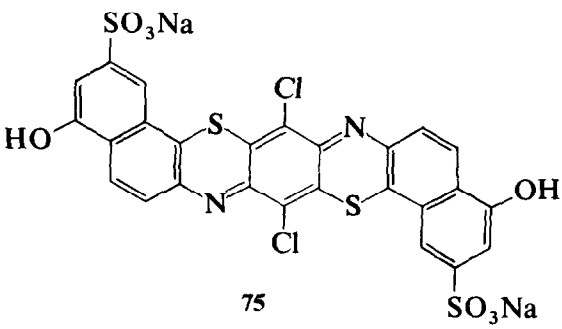


BzCl, $PhNO_2$
Δ, 5 h

76

Na_2S
H_2O, Δ



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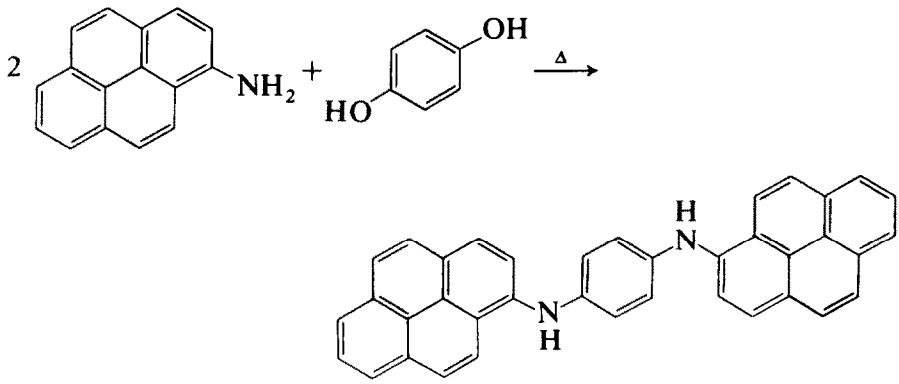

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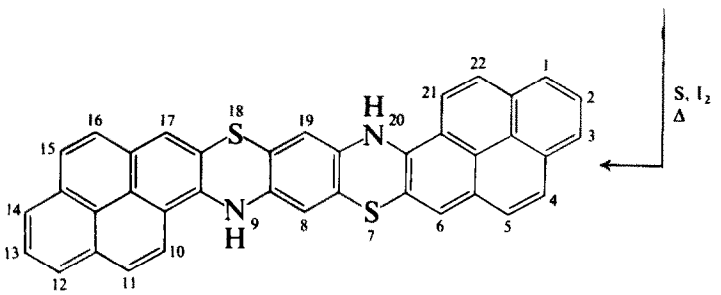


78

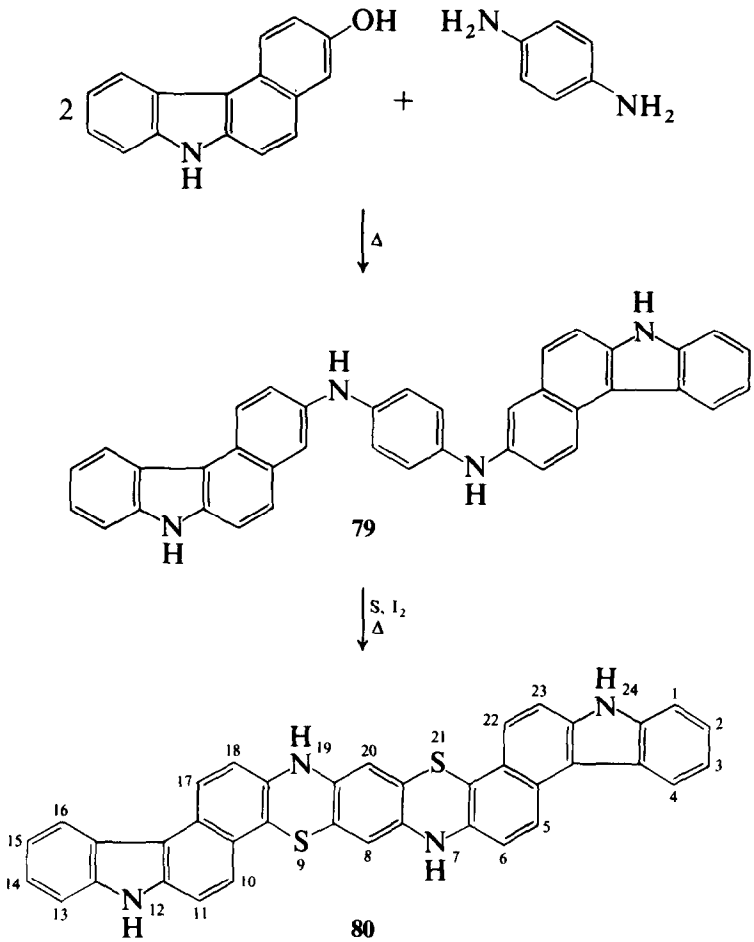
the presence of trace amounts of iodine to yield phenaleno[1,9-*ab*]pyreno[1′,2′:5,6][1,4]thiazino[3,2-*i*]phenothiazine (**78**).[60,61]

Compound **78** is the parent compound of this type of phenothiazine dye.

Carbazolo[3,4-*h*]carbazolo[4′,3′:7,8][1,4]benzothiazino[2,3-*b*]phenothiazine ring system (80)

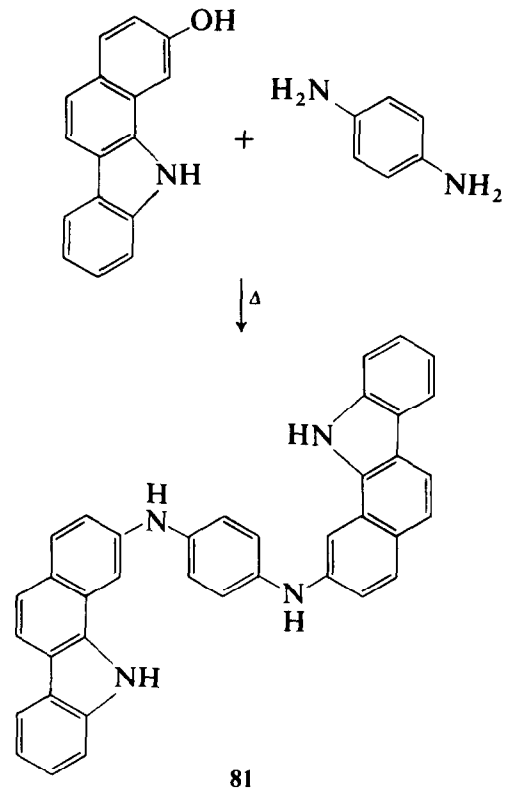
More complex polycyclic phenothiazines have also been made. Starting with 4-hydroxybenzo[*c*]carbazole and *p*-phenylenediamine which are converted by pyrolysis to *N*,*N*′-bis(4-benzo[*c*]carbazolyl)-*p*-phenylenediamine **79**, the desired carbazolo[3,4-*h*]carbazolo[3′,4′:7,8][1,4]benzothiazino[2,3-*b*]phenothiazine (**80**)[60,61] is obtained by the action of sulphur and catalytic amounts of iodine.

Product **80** is the parent compound of these ring systems and is a good dye for cellulosic materials.



Carbazolo[1,2-*h*]carbazolo[2′,1′:7,8][1,4]benzothiazino[2,3-*b*]phenothiazine ring system (82)

A dyestuff isomeric with compound **80** has also been prepared and commercially applied to cotton. Pyrolytic condensation of 2-hydroxybenzo[*a*]carbazole with *p*-phenylenediamine gave *N*,*N*′-bis(2-benzo[*a*]carbazolyl)-*p*-phenylenediamine (**81**). Cyclizative condensation of compound **81** with sulphur in the presence of iodine as a catalyst led to the polycyclic angular phenothiazine, carbazolo[1,2-*h*]carbazolo[2′,1′:7,8]-[1,4]benzothiazino[2,3-*b*]phenothiazine (**82**).[60,61]



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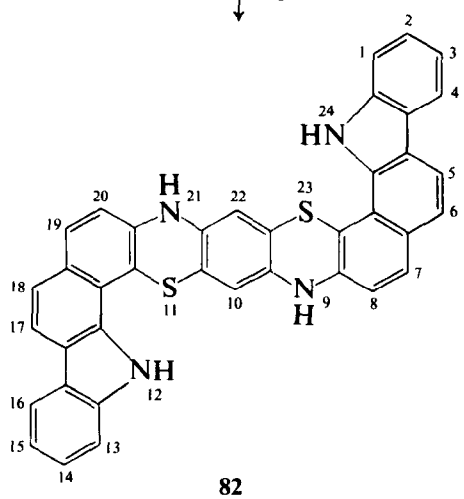


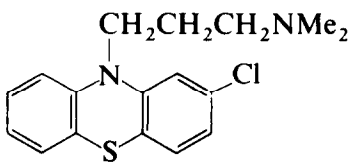
82

APPLICATIONS

Angular phenothiazines, being derivatives of phenothiazine, retain some properties associated with the parent phenothiazine ring system. This property is manifest in many of their medicinal properties. The anthelmintic,[62] antihistaminic and tranquilizing properties[63] of these compounds have been extensively investigated. Unlike the parent phenothiazine whose activity was above 90%, however, benzo[*a*]phenothiazine (**4**) (10–70% active) and dibenzo[*c*,*h*]phenothiazine (**10**) (< 10% active) were less active when tested for anthelmintic activity against infections of *Syphacia obvelata* and *Aspiculuris tetraptera* in mice.[64] It was found that no phenothiazine derivative with substituents at both the 3- and 7-positions was active but phenothiazine and some of its 3-substituted derivatives showed anthelmintic activity.

Phenothiazine *S*-oxides and *S*-dioxides were inactive, suggesting the importance of the availability of free *n*-electrons in the sulphur atom. With the exception of 10-formylphenothiazine, substitution at the 10-position gave inactive compounds. These results indicate that in the active 3-substituted derivatives, free 7- and 10-positions are necessary for anthelmintic activity. The activity is confined to compounds with oxidation–reduction potentials of 550–850 mV. The formation of a stable semiquinone radical by a univalent step is found to be a requirement for anthelmintic activity. The role of the phenothiazine derivatives is probably therefore to transfer electrons into the respiratory system of the parasite through the cuticle. A similar charge-transfer process was proposed by Karreman and Foster for the tranquilizing activity of phenothiazine derivatives.[65–67]

In a study of the mechanism of action of neuroleptic drugs, undertaken by Gozsy and Kato,[63] benzo[*c*]phenothiazine was found to be a much weaker neuroleptic agent than chlorpromazine (**83**) and promethazine (**84**).



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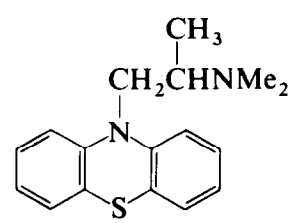
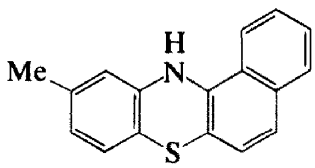


84

The effect of benzo[*c*]phenothiazine derivatives on dextran-induced edema was also investigated by Kato and Gozsy.[68] In rats injected intraperitoneally with dextran, the active angular phenothiazines inhibited the fall of blood pressure while also inhibiting the accumulation of carbon particles from injected India Ink at the sites of histamine. They particularly inhibited the increase in capillary permeability and delayed or even prevented the development of edema. The edema-delaying effect was directly proportional to the dose of the drug.

In view of the concern for the ever increasing incidence of cancer, the screening of a wide range of compounds is being undertaken. Buu-Hoi screened about 240 compounds[69–71] including benzo[*a*]phenothiazine (**4**), benzo[*c*]phenothiazine (**5**) and their derivatives. One of the highlights of this work is the apparent lack of carcinogenic activity of 10-methylbenzo[*a*]phenothiazine (**85**) and dibenzo[*c*,*h*]phenothiazine (**10**).[71] When compared with such polycyclic aromatic compounds as benzo[*a*]pyrene (**86**) and 9-methylbenz[*c*]acridine (**87**) the angular phenothiazines tested are apparently non-carcinogenic.



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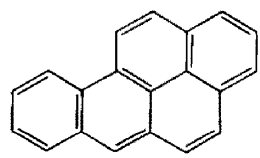

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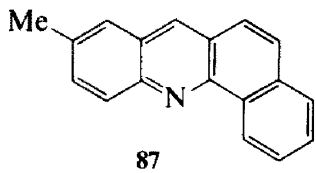
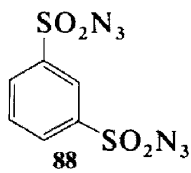


87

Light-sensitive photocopying materials have been made using benzo[*c*]phenothiazine. Irradiation of a mixture of benzo[*c*]phenothiazine (**5**) and compound **88** in 3 % aqueous ethylhydroxyethylcellulose gave dark green images on a yellow background.[72]



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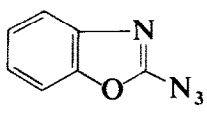
Similar preparations using benzo[*a*]phenothiazines (**4**) as couplers and using other organic azides of the types ArN_3, $ArCON_3$ and $ArCH{=}CHCON_3$ gave equally light-sensitive photographic elements suitable for films, plates, photographic printing papers and photocopying papers.[73] Phenothiazine (**1**) has also a similar property. Photographic products suitable for providing directly visible images have also been made using a conventional support coated with a colloidal layer containing the dissolved or dispersed photosensitive compound and a coupling agent. As photosensitive component of the colloidal layer, it was found that 2-azidobenzoxazole (**89**), 2-azidobenzimidazole (**90**) and 2,4-diazido-6-methylpyrimidine (**91**) were suitable.[74] The aroyl azides and their vinyl homologues were however less active.



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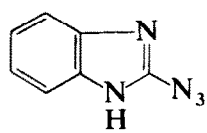

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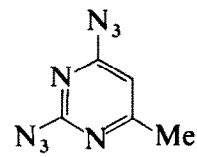
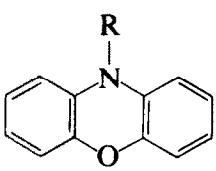


91

As coupling agents, phenoxazine (**92**, R = H) and its 10-alkyl derivatives (**92**), phenothiazines (**1**), benzo[*a*]phenothiazine (**4**), 2-azidobenzoxazole (**89**) and benzo[*b*]phenoxazine (**93**) can be used.



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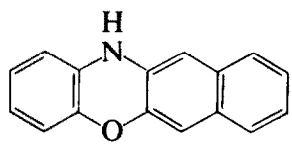

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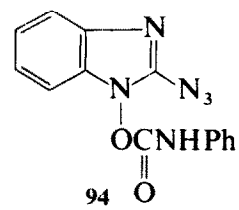
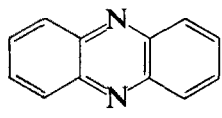


94

Photosensitive supports were made by dissolving the azide, the coupling agent and cellulose triacetate in CH_2Cl_2/MeOH mixture and drying the slurry as a plate. In another preparation, a paper is coated with a mixture of 50 g of 10% Vinylite VYLF solution in 2-butanone, 1 g of 2-azido-1-phenylcarbamoylbenzimidazole (**94**) and 0·3 g benzo[*b*]phenoxazine (**93**). Other suitable azide–heterocyclic base compositions are compounds **89** and **4**. As an example, a positive reddish violet image[74] was obtained

by exposure through a negative of a paper coated with 5% poly(butyraldehyde vinyl acetal) in methanol saturated with 2-aminobiphenyl hydrochloride and containing equivalent amounts of phenothiazine and benzoyl azide. The coloured image was stabilized by washing with hot water for 5 min.

Phenothiazine and benzo[*c*]phenothiazine (**5**) have been used successfully as indicators for polyester cross-linking.[75] Mixtures containing an unsaturated resin and 20–50% by weight of a monomer can be polymerized at 15–45 °C in mixtures containing 0·01–0·5 wt % indicator. The indicator determines the distribution of reactants and catalyst. The catalysts used were phenothiazine (**1**), benzo[*c*]phenothiazine (**5**), *p*-aminodiphenylamine and phenazine (**95**). Also added are 0·005–0·5 wt % of resin as stabilizer and 0·1–1·5% of a promoter to suppress the inhibiting action of the indicator. 1,2-Di(2-naphthylamino)benzene (**96**) is used as the indicator.[75]



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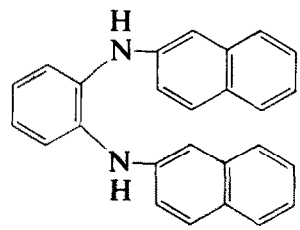

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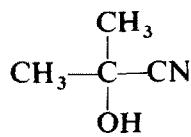
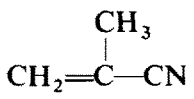


97

Polymerization is however retarded in the production of methacrylates by the reaction of acetone cyanohydrin **97** or methacrylonitrile (**98**), fuming sulphuric acid and ethanol in the presence of 3×10^{-3} to 1 % of benzo[*a*]phenothiazine (**4**) or benzo[*c*]phenothiazine (**5**) as retardant.[76]



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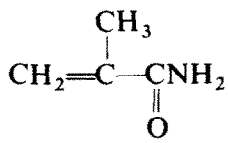

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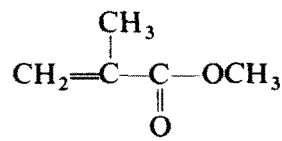

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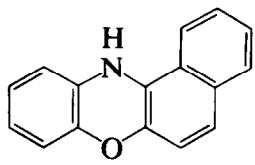
As an illustration, 86·3 g of compound **97** was added to 147 g of 98·5 % H_2SO_4 and 0·05 g of compound **4** or **5**. The mixture was stirred for 20 min below 70 °C and later heated to 140 °C in 10 min and maintained at this temperature for a further 10 min during which methacrylamide (**99**) sulphate is formed. Methanol (51·2 g) and 48·6 ml of water were added

and the entire mixture refluxed at 80 °C for 4 h and steam-distilled to give methyl methacrylate (**100**) containing only $1{\cdot}5 \times 10^{-2}$ g of the polymer, poly(methyl methacrylate), if benzo[*c*]phenothiazine (**5**) is used as the retardant. In the absence of a retardant, 18×10^{-2} g of poly(methyl methacrylate) was obtained. If 0·14 g of hydroquinone were used as the retardant, however, 72×10^{-2} g of the polymer was obtained. Other retardants used were 12*H*-benzo[*a*]phenoxazine (**101**) and 7*H*-benzo[*c*]phenoxazine (**102**) and the derivatives of compounds **4** and **5**.



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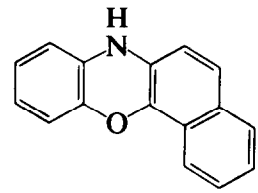
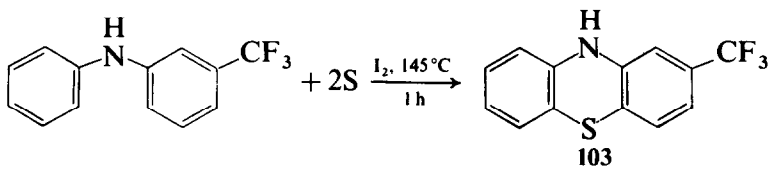


102

One of the main commercial uses of phenothiazine and benzophenothiazines is as antioxidants in gasoline and petroleum lubricants. 2-Trifluoromethylphenothiazine (**103**) and 3-isopropoxyphenothiazine (**104**) are good low-temperature antioxidants for gasoline and petroleum lubricants.



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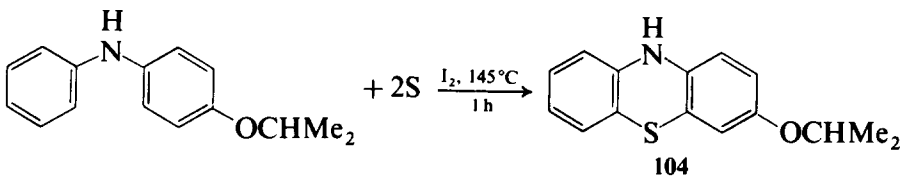
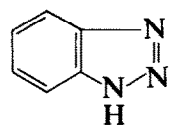


104

Benzo[*c*]phenothiazine-7-propionitrile[36] is now used commercially as an antioxidant for gasoline and petroleum lubricants such as engine oil. These phenothiazine derivatives are generally used for fuels for internal combustion engines in amounts varying from 1×10^{-3} to 100×10^{-3} wt %.[77] The additives act as polymerization inhibitors.

Aircraft gas-turbine engines require lubricants which have a flash point of at least 400 °F (195 °C), a viscosity at −40 °F (−40 °C) of less than 15 000 centistokes and a minimum viscosity of 7·5 centistokes at 210 °F (100 °C). Compositions of such lubricants[78] include a benzo-[*a*]phenothiazine having a decomposition temperature of at least 200 °C and a chlorinated polyphenol. In addition to the above, other esters of high thermal stability may be added. These include pentaerythritol tetracaproate. A satisfactory lubricant was made from bis(2-ethylhexyl) sebacate (68·2%), Ucon LB-1145 (28·5%), phenothiazine (**1**) or benzo[*a*]phenothiazine (**4**) (1%), Aroclor 4465 (2%), C.P.S. concentrate (0·25%) and benzotriazole (0·05 wt%) (**105**).



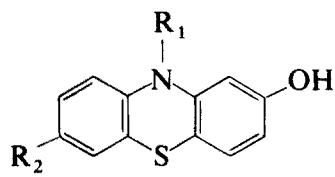
105

Benzo[*a*]phenothiazin-5-ones are commercially used as antioxidants for neoprene rubber.[74]

Benzo[*a*]phenothiazines are also used as antioxidants for stabilizing lubricating greases,[80] which consist of the lubricating fluid gelled with an alkali metal soap to which the antioxidant (0·1–3 wt%) is added. The lubricating fluid is mineral oil or mixtures of such oil with bis(2-ethylhexyl) sebacate. In addition to benzo[*a*]phenothiazine, a dialkyl telluride or selenide is also added in 0·1–3 wt%. Didodecyl selenide is the preferred selenide.

Vitamin A palmitate pills containing lactose and 4% 2-hydroxyphenothiazine (**106**, $R_1 = R_2 = H$) retained 76·2% of their potency after ten days while those prepared by the addition of the same amount of dihydronorguaiaretic acid retained only 24·2% of their potency in three days and after six days they lost all their potency.

In addition to the use of 2-hydroxyphenothiazine (**106**, $R_1 = R_2 = H$) as a stabilizer[81] for vitamin A, the use of 2,7-dihydroxyphenothiazine

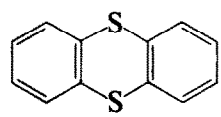


106

(**106**, $R_1 = H$, $R_2 = OH$), benzo[*a*]phenothiazine or 2-hydroxy-10-acetylphenothiazine (**106**, $R_1 = Ac$, $R_2 = H$) has been reported.[82]

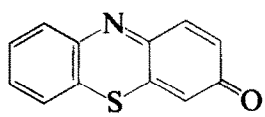
Polyolefins, polystyrene and copolymers of olefinic hydrocarbons can be stabilized[76,83] against oxidation by the addition of up to 1 wt% of phenothiazine or benzo[*a*]phenothiazine (**4**).

In further studies with phenothiazine, benzo[*c*]phenothiazine and several derivatives of phenothiazine, it was found that at relatively low concentrations (2×10^{-2} to 50×10^{-2} wt%) these compounds inhibited viscosity changes and acid production in pure bis(2-ethylhexyl) sebacate, which is utilized as a turbo-jet lubricant. Further work to determine the upper limit of inhibition showed that with phenothiazine the acid production and viscosity changes were negligible from 100 to 150 °C. At 175 °C, a small amount of coloured material indicated some volatilization. Lacquer deposition on the metals commenced at 150 °C and became pronounced with increase in temperature. The concentration of phenothiazine required for inhibition was 2×10^{-2} wt% at 125 °C and 94×10^{-2} wt% at 175 °C. Benzo[*c*]phenothiazine and derivatives of phenothiazine behaved similarly but at 175 °C comparatively little inhibition was observed compared with phenothiazine. Although phenoxazine (**92**, R = H), phenazine (**95**) and thianthrene (**107**) have antioxidant properties, they too were inferior to phenothiazine (**1**).



107

The antioxidant properties of phenothiazin-3-one (**108**) and phenothiazine-5-oxide (**109**) are comparable to that of phenothiazine itself. 3-Methylphenothiazine and benzo[*c*]phenothiazine (**5**) also gave very



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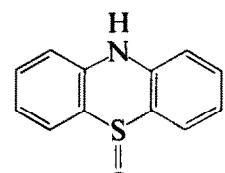
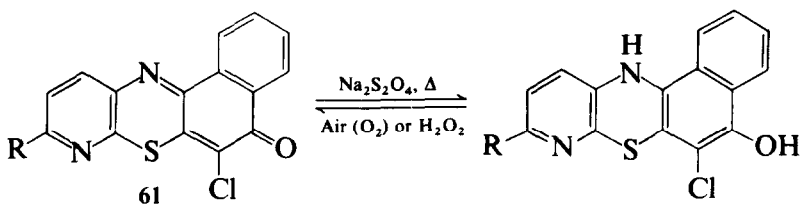


109

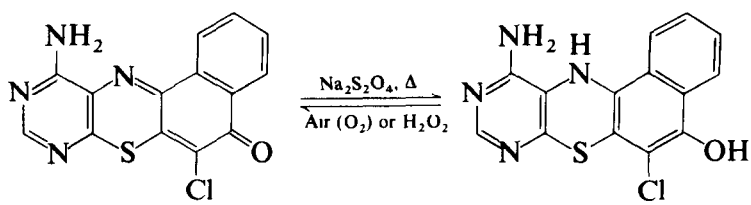
satisfactory antioxidant effects.[84] None of the diarylamines tested had antioxidant activity above 150 °C except 1-anilinonaphthalene (**13**).

Interest in angular phenothiazines at the beginning of the 20th century has been due to their applicability as dyes and pigments for paint and textile industries,[59-61] and it can be seen as being sustained due to recent reports in the literature. The discovery of a cheap method of preparing the precursor, 2,3-dichloro-1,4-naphthoquinone (**17**)[24] (available from Aldrich Chemical Co. Ltd, Milwaukee, Wisconsin, USA and Alpha Chemical Products, Danvers, Massachusetts, USA) and its ease of reaction with *o*-aminothiophenols have kept interest alive.

A wide range of colours varying from brown to purple[55] was recently reported for the angular azaphenothiazin-5-ones. Reduction with sodium hydrosulphite gave the azaphenothiazin-5-ols, which were too unstable to be isolated in the pure form as they undergo autoxidation in atmospheric oxygen to the quinoid systems.



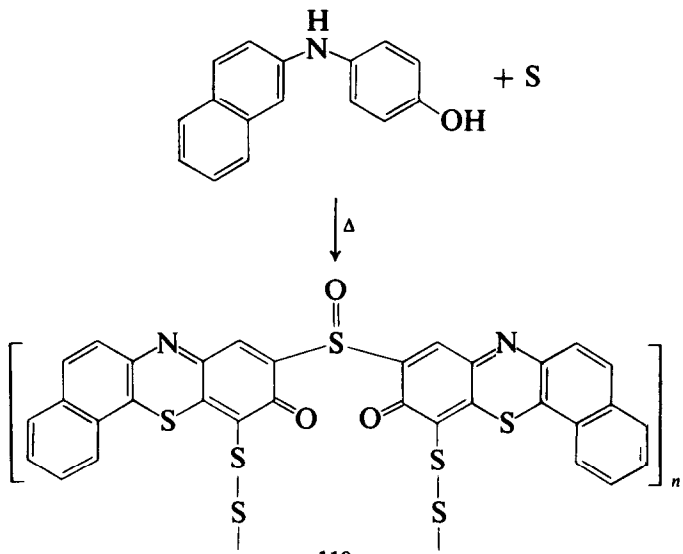
R = H (brown)
R = Cl (red)
R = OMe (bluish-red)



12*H*-Benzo[*a*]phenothiazine (**4**) reacts with some heterocyclic azides under the influence of heat or light to give azomethine dyes[85] in which the coupling occurs at the 5-position of compound **4**. Owing to this property, these angular aza- and diaza-phenothiazines may be applied as vat dyes for the textile industries.

Many polycyclic angular phenothiazines have been prepared and used as dyes. Notable among these are derivatives of compounds **88** to **96**. Some specific sulphur dyes which are polymers of benzo[*c*]phenothiazin-3-one monomer are also in use. The indocarbon **110**, a specific sulphur

dye,[86] is synthesized by the action of elemental sulphur on *N*-(*p*-hydroxyphenyl)-2-naphthylamine. It is believed to have the complex structure shown.



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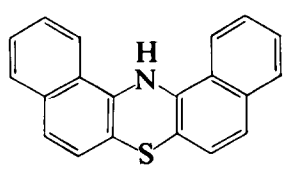
Polarographic[87] and magnetic susceptibility measurements[88] have been carried out for these angular phenothiazines, their *S*-oxides and *S*-dioxides. Resonance effects were detected comparable to those found calorimetrically. Magnetic susceptibility measurement for dibenzo-[*a*,*c*]phenothiazine (**11**) is $186{\cdot}5 \times 10^6\,g^{-1}$ compared with $101{\cdot}8 \times 10^6\,g^{-1}$ for 1-naphthylamine, $99{\cdot}1 \times 10^6\,g^{-1}$ for 2-naphthylamine and $86{\cdot}0 \times 10^6\,g^{-1}$ for quinoline. A detailed study of the infrared spectra of phenothiazine (**1**), benzo[*a*]phenothiazine (**4**), benzo[*c*]phenothiazine (**5**), dibenzo[*a*,*h*]phenothiazine (**9**), dibenzo[*a*,*i*]phenothiazine (**111**), dibenzo[*c*,*h*]phenothiazine (**10**) and their *S*-oxides and *S*-dioxides were investigated[89] in the region of NH and S=O vibrations.



111

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