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Synthesis, Properties and Uses of Angular Phenoxazines

C. O. Okafor

Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Nigeria

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SUMMARY

Since the first and prototype of angular phenoxazines, Meldola Blue, was reported over a century ago, several hundreds of derivatives have so far been made. These include the side-chain derivatives, isomeric structural types and the aza-, thia- and oxa-analogues. Some naturally occurring angular azaphenoxazines have also been isolated from arthropods. Most of the natural compounds in these series are intensely coloured and are responsible for the coloration in the wings, cuticle and eyes of insects.

In general, angular phenoxazines constitute an important class of organic compounds because of their wide range of commercial uses. These include their uses as drugs, polymerization retardants, photosensitizers, acid–base indicators, redox indicators, biological stains, metal extractants and, most importantly, as dyes and pigments for the textile, paint and varnish industries.

In this article, the first comprehensive report on the chemistry and industrial applications of angular phenoxazines is presented.

1. INTRODUCTION

The chemistry of phenoxazine (**1**) and its aza-analogues has been extensively studied and many review articles on it have appeared, notably the reports by Pearson,[1] Ramage,[2] McKee,[3] Schaefer,[4] Ionescu[5] and Okafor.[6] In these papers the natural occurrence of some phenoxazine derivatives and their commercial uses were highlighted.

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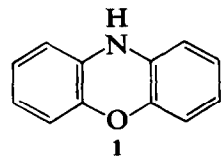
No comprehensive review of the angular derivatives of phenoxazine has however been made, even though such compounds have been known for nearly a century now. In view of the importance of angular phenoxazines, particularly as chemotherapeutic agents, antioxidants, acid–base and redox indicators, and as dyes and pigments, we present here the chemistry and applications of these heterocyclic compounds.



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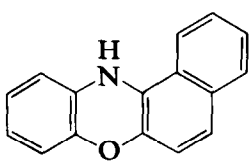
Angular phenoxazines may be defined as those polynuclear phenoxazines which have a non-linear arrangement of the ring system. By this definition, they include the following ring systems: benzo[*a*]phenoxazine (**2**); benzo[*c*]phenoxazine (**3**); dibenzo[*a*,*i*]phenoxazine (**4**); dibenzo[*a*,*j*]-phenoxazine (**5**); dibenzo[*a*,*h*]phenoxazine (**6**); pyrido[3,2-*a*]phenoxazine (**7**); benzo[*a*]-11-azaphenoxazine (**8**); and [1]benzopyrano[3,4-*b*]-benzoxazine (**9**).



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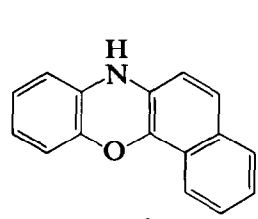

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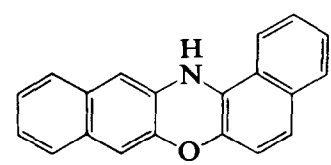

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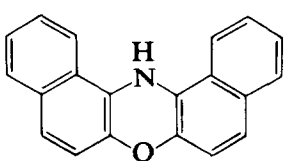

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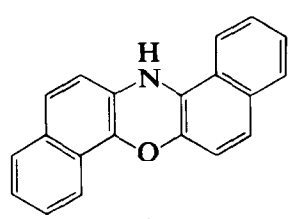

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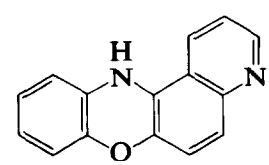

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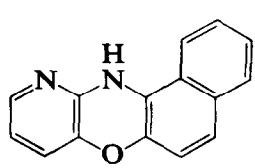

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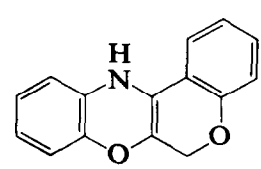

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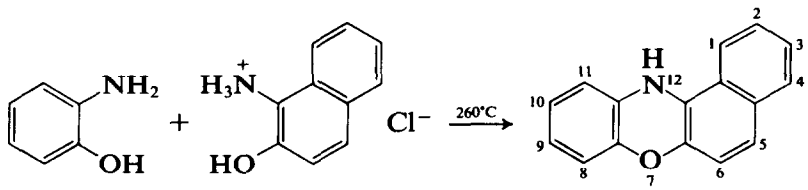
2. ANGULAR PHENOXAZINES

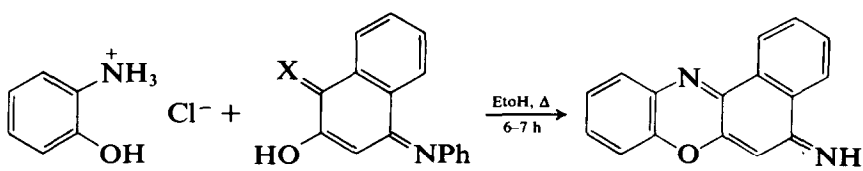
Benzo[*a*]phenoxazine

The simplest angular phenoxazine, benzo[*a*]phenoxazine (**2**), was first reported by Goldstein and Semelitch in 1919 during their search for new phenoxazine dyestuffs.[7]



10 **11** **2**

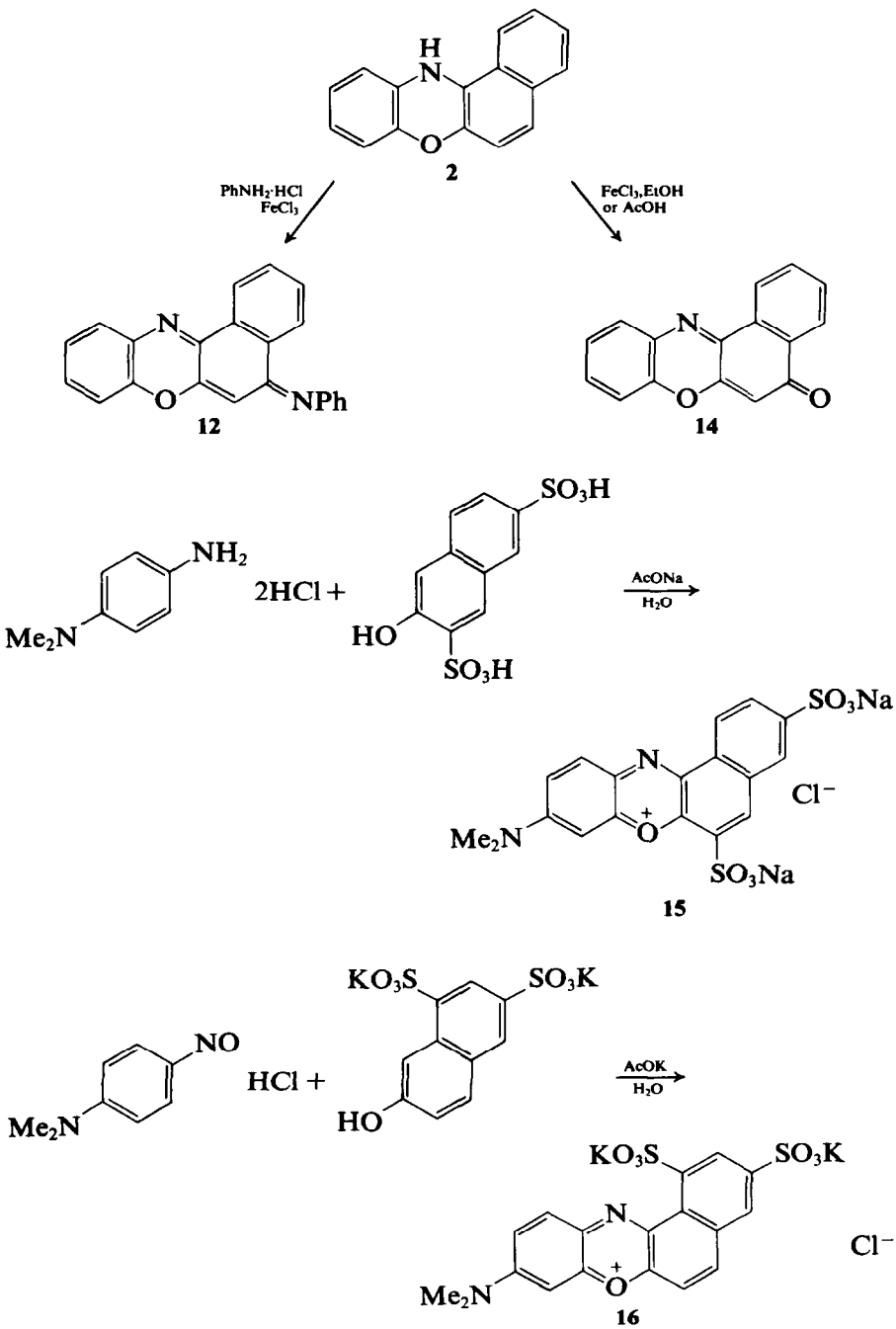
The parent benzo[*a*]phenoxazine (**2**) was obtained by these workers by the pyrolysis of *o*-aminophenol (**10**) admixed with 1-amino-2-naphthol hydrochloride (**11**) at 260 °C. The product is a yellow solid (m.p. 107 °C (dec)) with an intense green fluorescence in ethanolic solution. The more intensely coloured quinoid angular phenoxazinone, **12**, was prepared by refluxing a mixture of *o*-aminophenol hydrochloride and the anilinonaphthoquinone, **13**, X = O, for 6–7 h. The same product, **12**, was also obtained by condensing compounds **10** and **13**, X = NPh, in refluxing methanol, pyridine or nitrobenzene in the presence of a copper salt.[8]



13 **12**

Product **12**, an orange solid melting at 215 °C, was also obtained by treating compound **2** with aniline hydrochloride followed by the action of excess ferric chloride as the oxidizing agent. Oxidation of benzo[*a*]phenoxazine with ethanolic ferric chloride gave benzo[*a*]phenoxazin-5-one (**14**), showing that the 5-position is the centre which is most susceptible to oxidation.

Two indicators, **15** and **16**, suitable for use in redox titrations, were prepared by Eggers and Dieckmann[9] by cyclizative condensation of some aniline derivatives with hydroxynaphthalene sulphonic acids.


H
N
O
2
PhNH2·HCl
FeCl3
FeCl3,EtOH
or AcOH
N
O
NPh
12
N
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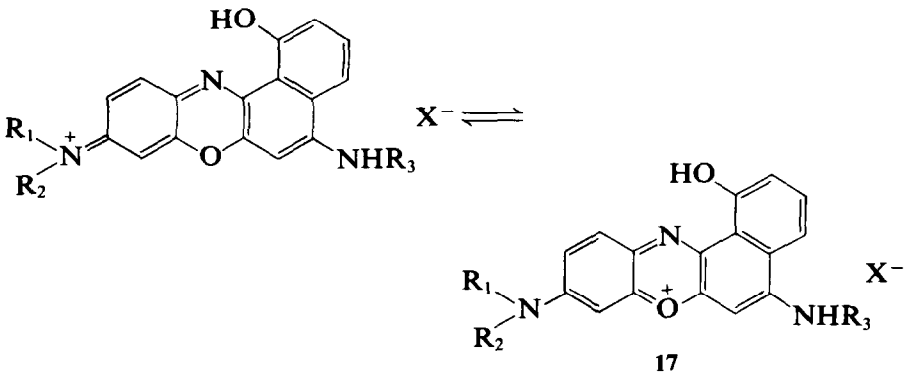
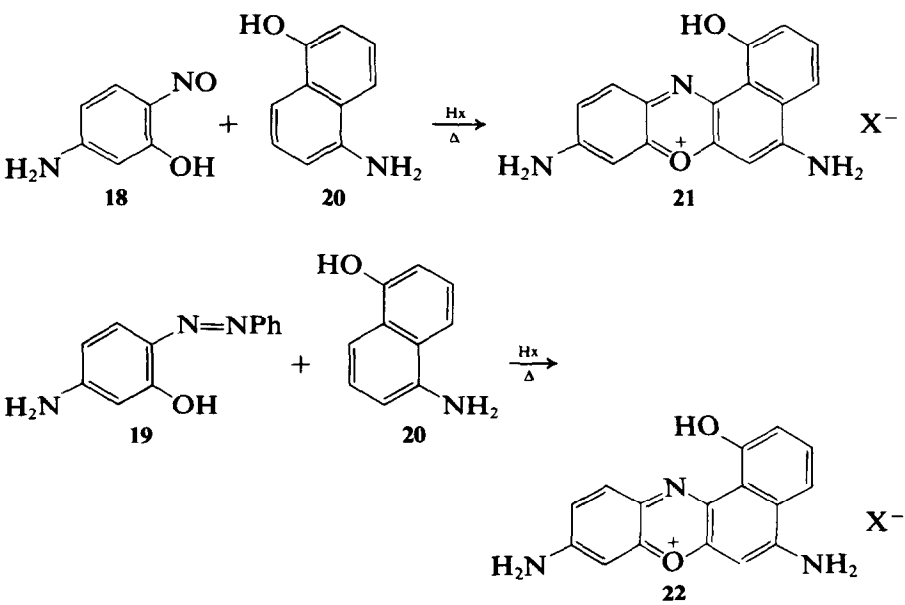
O
14
NH2
Me2N
2HCl +
SO3H
HO
SO3H
AcONa
H2O
SO3Na
N
O+
Cl−
Me2N
SO3Na
15
NO
Me2N
HCl +
KO3S
SO3K
HO
AcOK
H2O
KO3S
SO3K
N
O+
Cl−
Me2N
16

Fibres, filaments, fabrics and moulded articles made of acrylonitrile polymers or acrylonitrile copolymers containing 85% acrylonitrile are dyed and printed with aminobenzo[*a*]phenoxazines[10] of type **17**. The



17

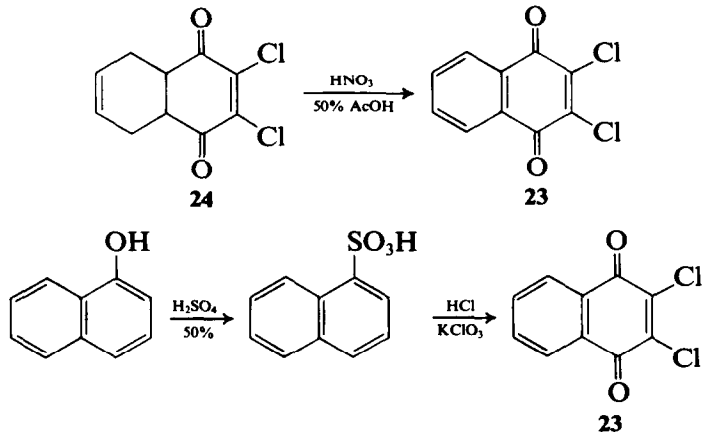
dyes were obtained by refluxing 4-nitroso-3-hydroxyaminobenzenes (**18**) or 4-amino-2-hydroxyazobenzenes (**19**) with 1-amino-5-naphthol (**20**). Dyeing was carried out in an aqueous solution by the addition of acetic, formic or sulphuric acid using, as the dispersing agent, a polyglycol ether of a high-molecular-weight aliphatic alcohol if needed. Good light-fastness was reported with this type of dye.[10]



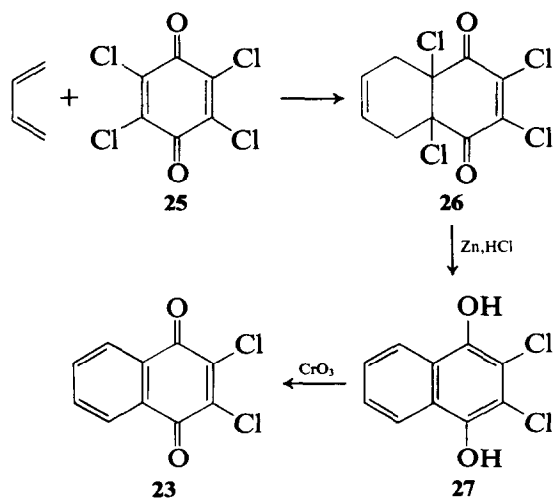
18 **20** **21**

19 **20** **22**

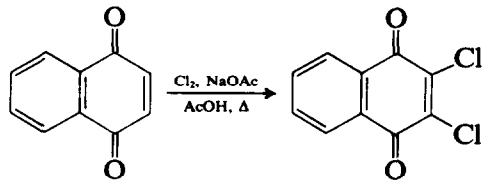
In more recent years, attention has been turned to those angular phenothiazines of type **2** which can be obtained from more readily available compounds. 2,3-Dichloro-1,4-naphthoquinone (**23**), which is a commercial fungicide for agriculture and for textiles,[11] was one of the first compounds to be considered. Coover and Dickey[12] prepared it by nitric acid oxidation of 2,3-dichloro-4a,5,8,8a-tetrahydronaphtho-1,4-quinone (**24**). Kiprianov and Stetsenko[13,14] obtained the same compound by



treating naphthol-1-sulphonic acid with HCl and $KClO_3$. Gaertner's method[15] involves the Diels–Alder reaction of butadiene with 2,3,5,6-tetrachloro-1,4-quinone (chloranil) (**25**) to form the bicyclic chloranil **26** which, in turn, is reduced with zinc and hydrochloric acid to yield compound **27**. Subsequent oxidation of compound **27** with chromic



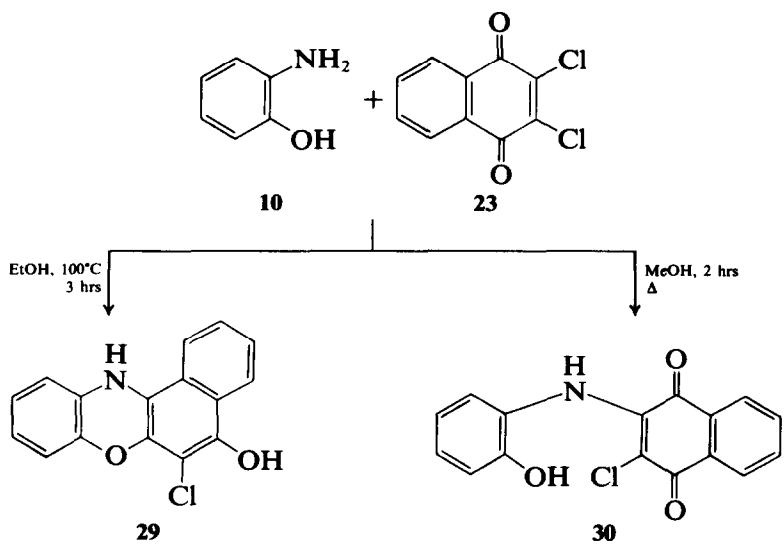
trioxide afforded product **23** in 71 % yield. The most successful procedure however was provided by Fieser[16] in 86% yield by chlorinating 1,4-naphthoquinone (**28**) with chlorine in the presence of anhydrous sodium acetate.



28 **23**

2,3-Dichloro-1,4-naphthoquinone is now commercially available, thereby making its use in the manufacture of dyes more economical.

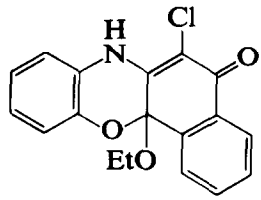
The reaction of *o*-aminophenol with 2,3-dichloro-1,4-naphthoquinone was pioneered by VanAllan and Reynolds,[17] who assigned structure **29** to the product of the reaction in ethanol. In methanol, a surprisingly different product, **30**, was reported by the same authors.[18]



10 **23**

29 **30**

Agarwal and Schafer,[19] who repeated this work, could not reproduce their results either in refluxing ethanol or methanol. None of the five compounds **31**–**35** isolated by them in 50 %, 11 %, 5 %, 3 % and 2 % yields respectively had the same structure as either of the compounds, **29** and **30**, reported by VanAllan and Reynolds. Agarwal and Schafer's results



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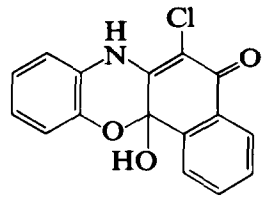

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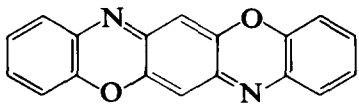

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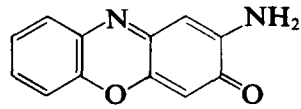

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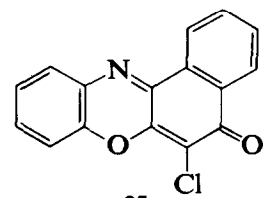

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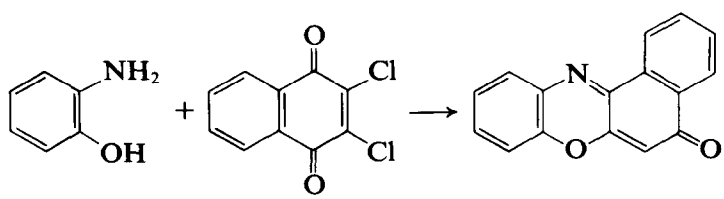
are supported by spectroscopic data and by the facts that (i) 5-hydroxybenzo[*a*]phenoxazines are generally unstable to air oxidation to the quinoid form **35** and (ii) it does not appear reasonable that the reaction will proceed by different mechanistic pathways in ethanol and methanol solvents.

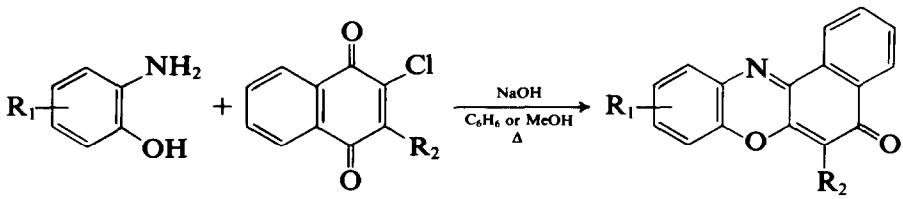
In non-aqueous alkaline media, however, compounds **10** and **23** reportedly[17] produce good yields of the chlorine-free 5*H*-benzo[*a*]-phenoxazin-5-one, **36**, in methanolic KOH. This unusual reductive dehalogenation reaction was reinvestigated by Agarwal and Schafer,[19]



10 **23** **14**

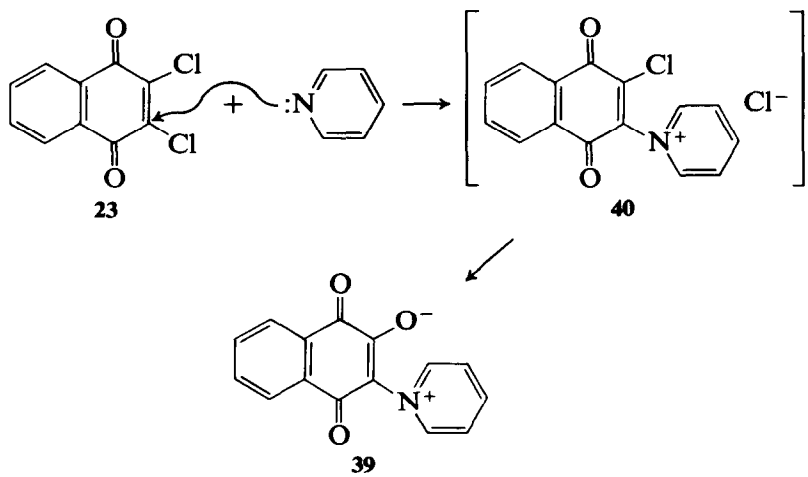
who isolated 6-chlorobenzo[*a*]phenoxazin-5-one (**37**; $R_1 = H, R_2 = Cl$) in 40% yield. In other words, reductive dehalogenation did not take place as was earlier claimed.[17] Base-catalysed condensation of *o*-aminophenols with 2-chloro-1,4-naphthoquinones (**38**; $R_2 = Cl$, NHR) has now become a standard method of producing a variety of benzo[*a*]phenoxazin-5-one dyes (**37**).

Another reactive naphthoquinone derivative, 1,4-dioxo-3-pyridinium-2-naphthoxide (**39**), similar in reactivity to compound **23**, was obtained[17,20] in near-quantitative yields by refluxing equimolar amounts



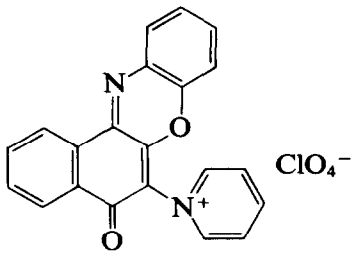
36 38 37

of 2,3-dichloro-1,4-naphthoquinone and dry pyridine in butanol. Presumably, pyridine undergoes nucleophilic attack at the 2-position of the naphthoquinone **23** leading to the elimination of chloride ion and formation of the pyridinium salt, **40**. The halogen in the 3-position now has enhanced reactivity as a result of the *-I* and *-M* effects of the pyridinium ion. Due to the high reactivity of this halogen, an attempt to recrystallize it from water or ethanol led to 1,4-dioxo-3-pyridinium-2-naphthoxide, **39**.[17] Both the adduct **40** and the transformed product



23 40 39

39 are reactive towards nucleophilic reagents and yield a variety of condensation products. Compound **40**, produced *in situ*, reacts with *o*-aminothiophenol to give a variety of compounds, namely, 5*H*-benzo[*a*]phenoxazin-5-one-6-pyridinium perchlorate (**41**, $X = ClO_4^-$), 5*H*-benzo[*a*]phenoxazin-5-one (**14**), 2-(2-hydroxyanilino)-1,4-naphthoquinone-3-pyridinium perchlorate (**42**, $X = ClO_4^-$) and 6-chloro-5*H*-benzo[*a*]phenoxazin-5-one (**35**) in 6%, 10%, 13% and 0·5% yields respectively.[21]



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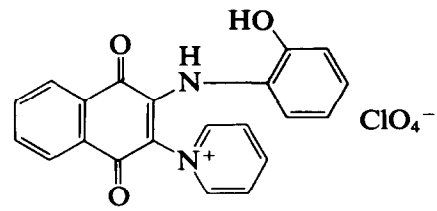
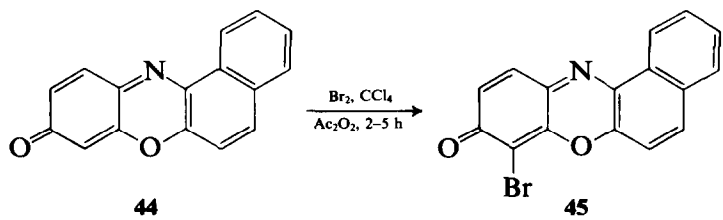


42

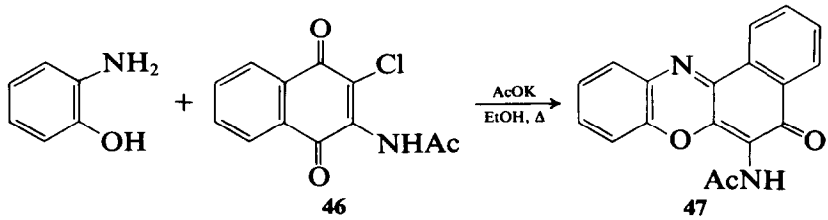
The mechanistic pathways to these products were formulated as shown in Scheme 1. Nucleophilic attack of the hydroxyl group in structure **42** on the naphthoquinone carbon atom attached to the pyridinium ion led to cyclization and formation of the novel 12*H*-benzo[*b*]phenoxazine-6,11-diones, **43** if R = an electron-withdrawing group.

Free radical bromination of benzo[*a*]phenoxazin-9-one (**44**) gave the 8-bromo derivative **45**.[22]



44 45

2-Acetamido-3-chloro-1,4-naphthoquinone (**46**) also condenses with *o*-aminophenol in ethanol in the presence of anhydrous potassium acetate to afford 6-acetamidobenzo[*a*]phenoxazin-5-one (**47**) in 80% yield.[23]



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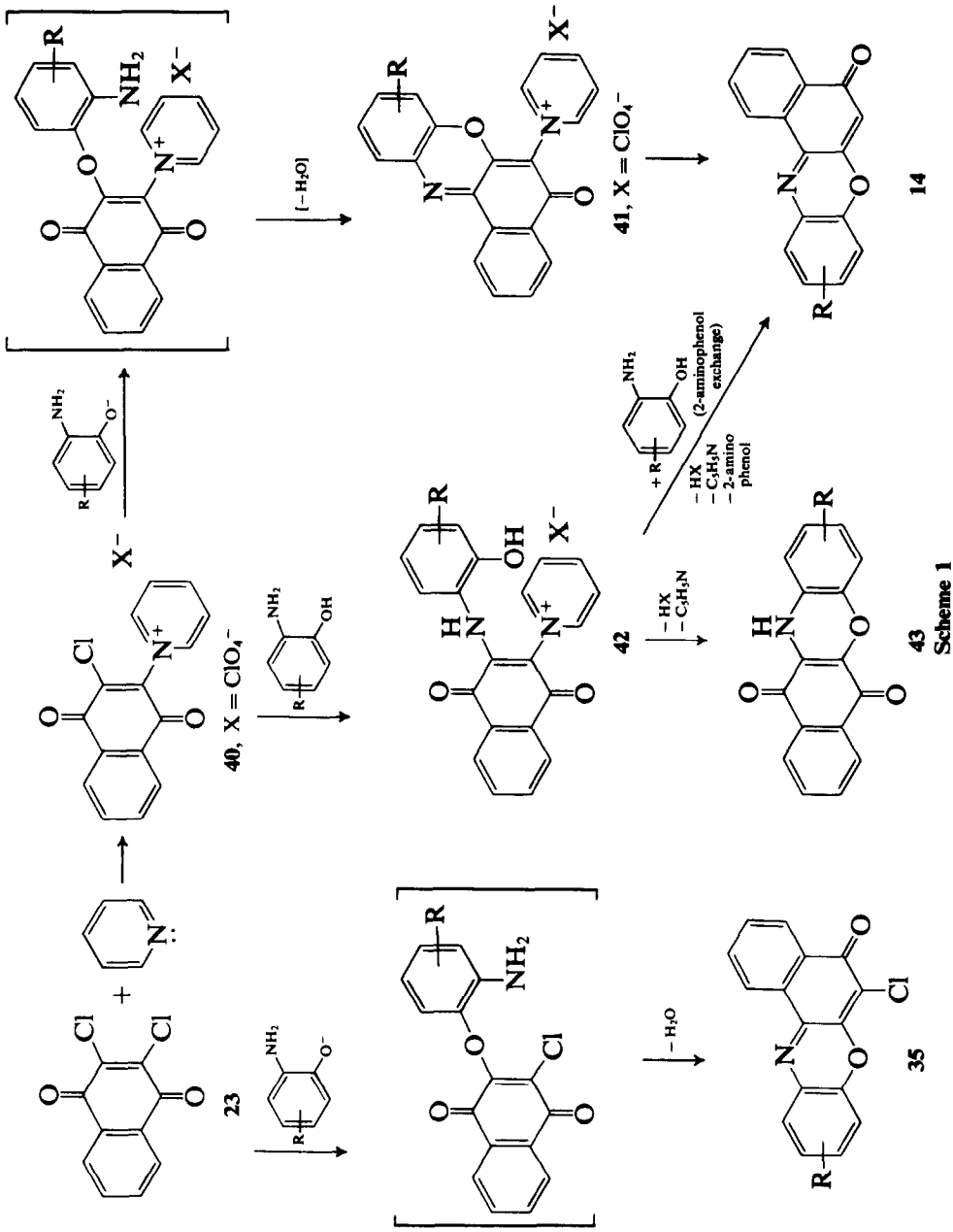
Benzo[*c*]phenoxazine

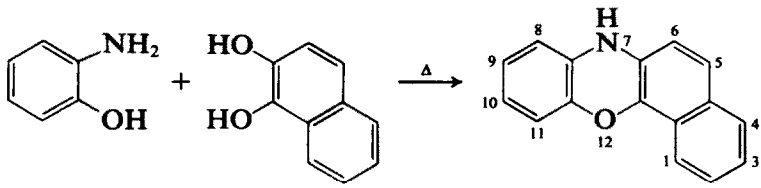
The chemistry of benzo[*c*]phenoxazine (**3**) is almost as old as that of its benzo[*a*]-isomer (**2**). The parent compound was first prepared by


23
40, X = ClO4-
41, X = ClO4-
42
43
14
35
- H2O
- HX
- C5H5N
+ R
- HX
- C5H5N
- 2-amino phenol
(2-aminophenol exchange)
[- H2O]

Scheme 1

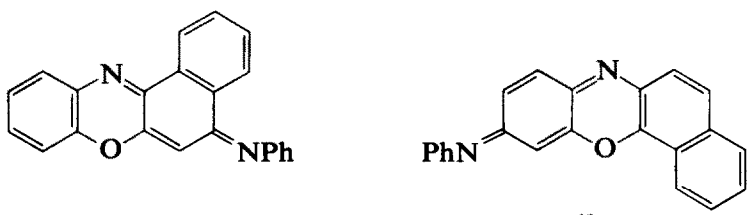
Kehrmann and Goldstein[7,24] by pyrolysis of *o*-aminophenol and naphthalene-1,2-diol (**48**).

Although two products, **2** and **3**, are expected from this reaction, only one product, namely compound **3** (m.p. 127–128 °C), was isolated.



10 **48** **3**

Treatment of this product with aniline hydrochloride and ferric chloride gave two basic materials[7] which were blue and red in colour after acidification with dilute HCl. The product which gave a red hydrochloride salt in HCl was identical with compound **12**. The other blue hydrochloride salt was identified as the hydrochloride of the benzo[*c*]-phenoxazine, **49**. The reaction of compound **3** with aniline hydrochloride



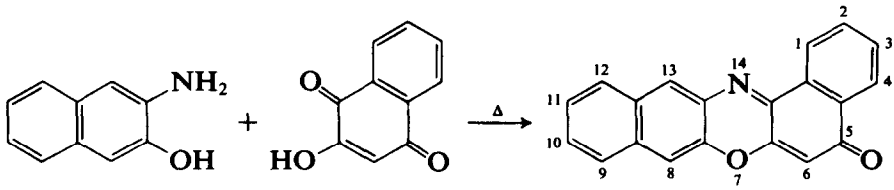
12 **49**

in the presence of ferric chloride is simply an oxidative condensation which does not involve rearrangement. Since compound **12** was also obtained during the reaction, it is obvious that the reported product **3** from the reaction of compounds **10** and **48** is actually a mixture with compound **2**. In other words, a mixture of benzo[*a*]phenoxazine (**2**) and benzo[*c*]phenoxazine (**3**) is actually formed in the original reaction of **10** and **48**.

Benzo[*c*]phenoxazine (**3**) gave, as compound **2** did, a green fluorescence in ethanolic solution. It is somewhat unstable to air oxidation and darkens on heating up to 100 °C.

Dibenzo[*a,i*]phenoxazine

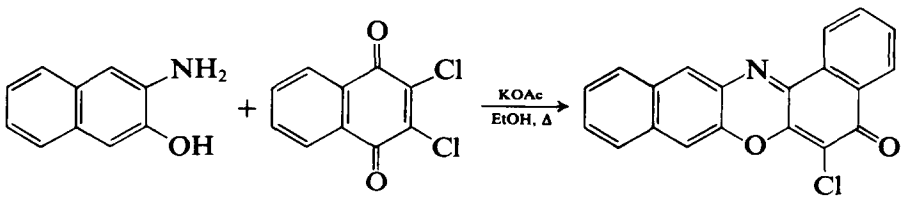
Dibenzo[*a,i*]phenoxazine (**4**) derivatives were first reported by Goldstein[25] in 1928. He obtained these compounds by heating strongly a



50 **51** **52**

mixture of 2-amino-3-naphthol (**50**) and 2-hydroxy-1,4-naphthoquinone (**51**).

Agarwal and Schafer[19] obtained 6-chloro-5*H*-dibenzo[*a*,*i*]phenoxazin-5-one (**53**) in 18% yield by refluxing a stoichiometric mixture of 2-amino-3-naphthol (**50**) and 2,3-dichloro-1,4-naphthoquinone **23** in the

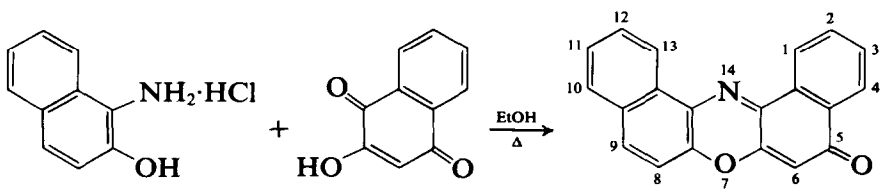


50 **23** **53**

presence of anhydrous potassium acetate in ethanol. The imines and other derivatives of compound **4** were also reported. These compounds, as expected, are intensely coloured and therefore are applicable as dyestuffs if other conditions are met.

Dibenzo[*a*,*j*]phenoxazine

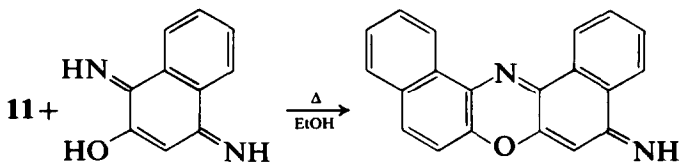
Further variation of the dibenzophenoxazine ring system was made by Goldstein when he reported some 5-derivatives of dibenzo[*a*,*j*]-phenoxazine (**5**). By heating a mixture of 1-amino-2-naphthol hydrochloride and 2-hydroxy-1,4-naphthoquinone in ethanol, dibenzo[*a*,*j*]-phenoxazin-5-one (**54**)[26] was obtained.



11 **51** **54**
(red in colour)

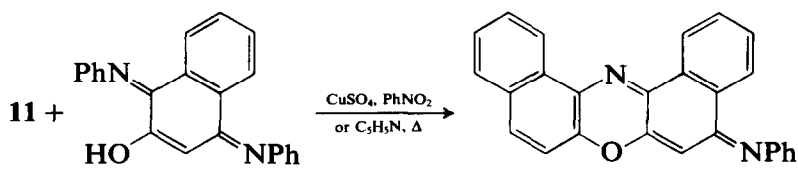
Compound **54**, m.p. 277–278 °C, is a red powder which gave colour changes with sulphuric acid on dilution. Its solution in organic solvents showed yellow fluorescence.

Compound **11** also reacts with 2-hydroxy-1,4-naphthoquinoneimine (**55**) to give green crystals of dibenzo[*a*,*j*]phenoxazine-5-imine hydrochloride (**56**).[26]



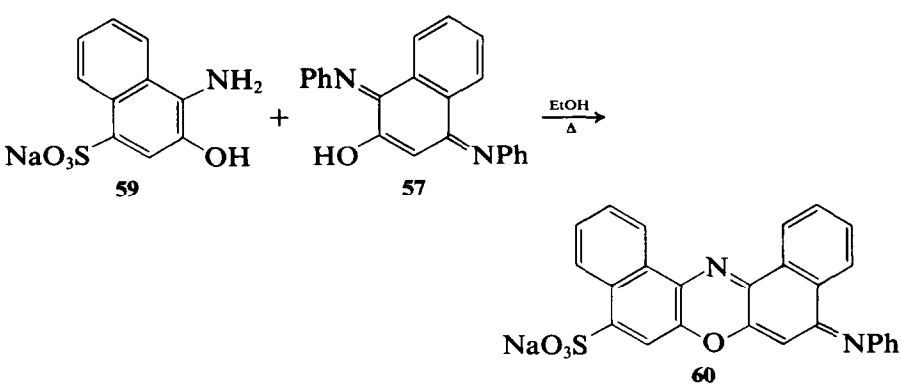
55 **56** (green in colour)

More derivatives of this ring system have also been reported. Lantz[8] obtained the *N*-phenyl-analogue of compound **56** by heating compounds **11** and 2-hydroxy-1,4-naphthoquinonephenylimine (**57**). To obtain more



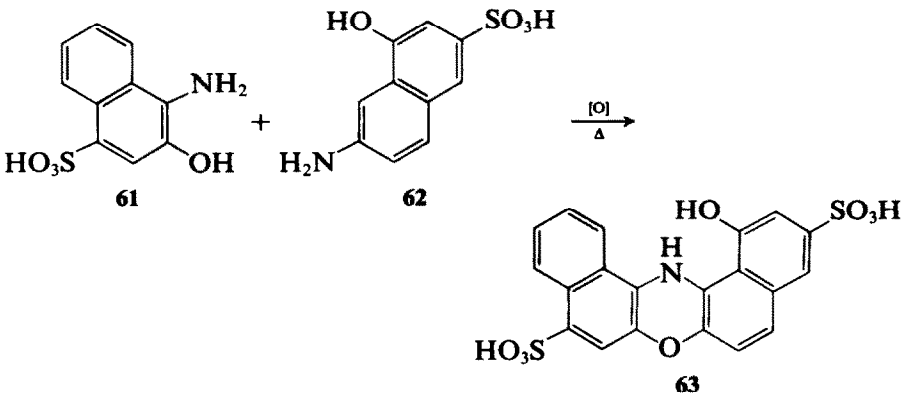
57 **58**

soluble dibenzophenoxazines of this type, compound **57** was condensed with sodium 1-amino-2-naphthol 4-sulphonate (**59**) to give sodium dibenzo[*a*,*j*]phenoxazin-5-phenylimine 9-sulphonate, **60**.[8]

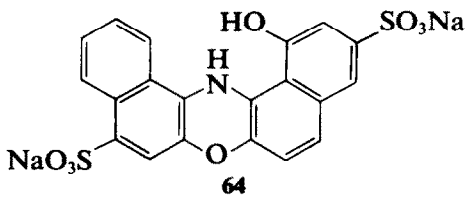


59 **57** **60**

A brown dye[27] with this ring system was prepared commercially by oxidative condensation of 1-amino-2-naphthol 4-sulphonic acid (**61**) with 2-amino-8-naphthol 6-sulphonic acid (**62**). The product, **63**, was

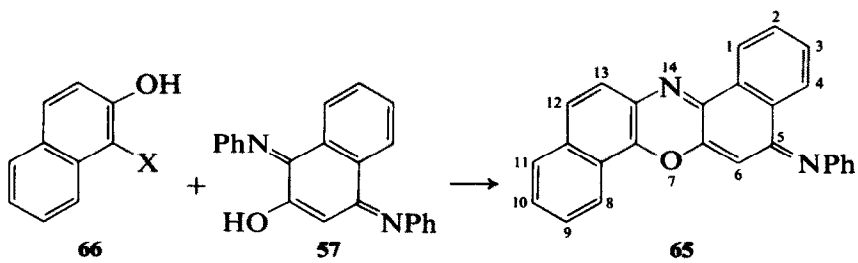


converted to the disodium salt, disodium 1-hydroxydibenzo[*a*,*j*]-phenoxazine 3,9-disulphonate (**64**), which is the brown dye of commercial importance. It has a great stability of colour and is easily absorbed from the dyebath by silk and wool.



Dibenzo[*a*,*h*]phenoxazine

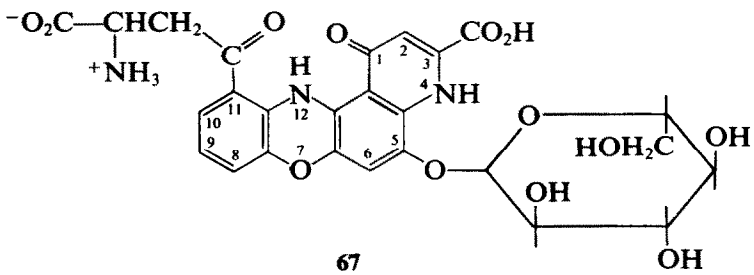
In continuation of a search for new and commercially useful compounds in the phenoxazine class, dibenzo[*a*,*h*]phenoxazine derivatives were also prepared. Lantz[8] obtained dibenzo[*a*,*h*]phenoxazin-5-phenylimine (**65**) by refluxing a mixture of 2-naphthol (**66**, X = H) and compound **57** in



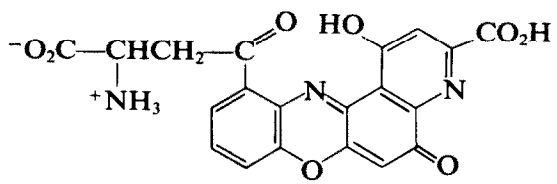
xylene. The same dye **65** (m.p. 321 °C) was obtained by condensing 1-bromo-2-naphthol (**66**, X = Br) with **57** in refluxing nitrobenzene.

Pyrido[3,2-*a*]phenoxazine

Interest in the aza-analogues of phenoxazine derivatives has grown tremendously since the dawn of the 20th century. Some angular aza-phenoxazines, particularly the pyrido[3,2-*a*]phenoxazines, occur in nature. The ommochromes, exemplified by rhodommatin **67**[6,28,29] and xanthommatin **68**, are responsible for the coloration in the wings of insects of



67



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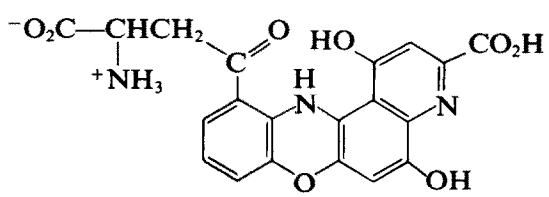
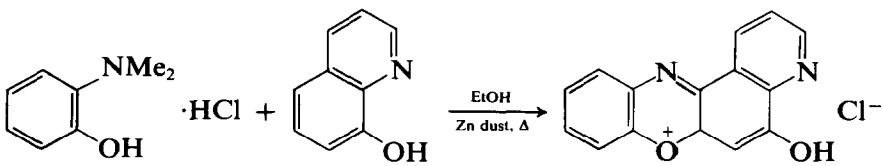


69

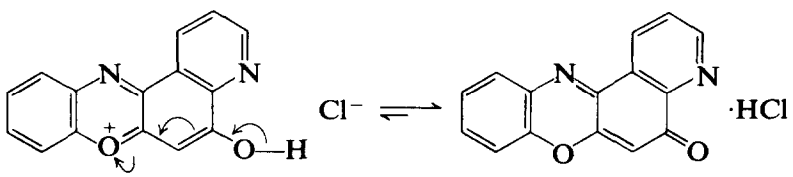
the Lepidoptera family. Xanthommatin is also found as an eye pigment in insects. It occurs in the secretions of *Vanessa urticae* and the eyes of the blowflies *Calliphora erythrocephalla* and *Musca domestica*. The pigments of the testis and the eyes of the butterfly *Papilio xuthus* were examined by some Japanese workers. The red pigment found in the testis was identified as dihydroxanthommatin (**69**). In the eyes, the reddish-brown xanthommatin and other purple ommochromic pigments were identified.[30]

In addition to the chemistry of naturally occurring pyrido[3,2-*a*]-phenoxazines, the synthesis of compounds with this ring structure was reported by Noelting[31] in 1922. He obtained the blue dye **70** by the reaction of 8-hydroxyquinoline with *o*-hydroxy-*N*,*N*-dimethylaniline hydrochloride in the presence of a trace of zinc. The structure of the



70

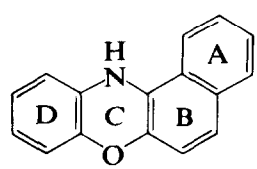
product of this reaction is likely to be the 5-oxo structure **71** rather than the hydroxy salt, **70**, because of the reported instability of 5-hydroxybenzophenoxazines and phenazines. This product is a good blue mordant dye for cotton mordanted with tannin and fixed by iron, aluminium or chromium mordant.



70 **71**

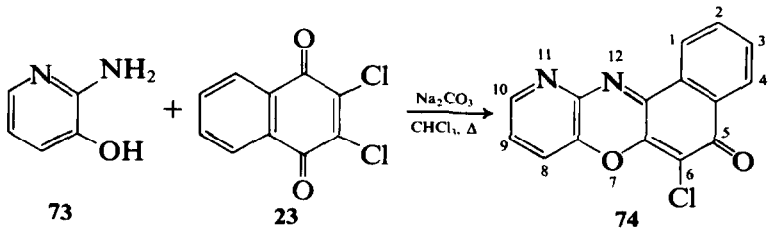
Benzo[*a*]-11-azaphenoxazine

In addition to the angular azaphenoxazines in which the annular nitrogen is in ring A, attempts have been made to synthesize the analogues in which the nitrogen is in ring B or D (structure **72**).



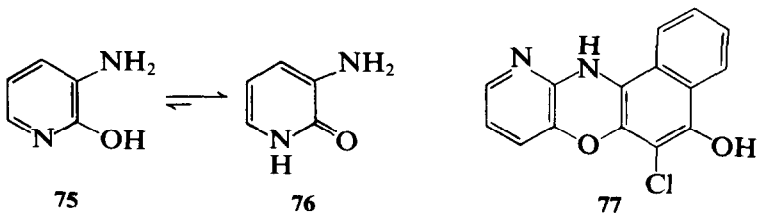
72

2-Amino-3-pyridinol (**73**) reacts with 2,3-dichloro-1,4-naphtho-quinone (**23**) in chloroform in the presence of anhydrous sodium carbonate to give 6-chlorobenzo[*a*]-11-azaphenoxazin-5-one (**74**) in good



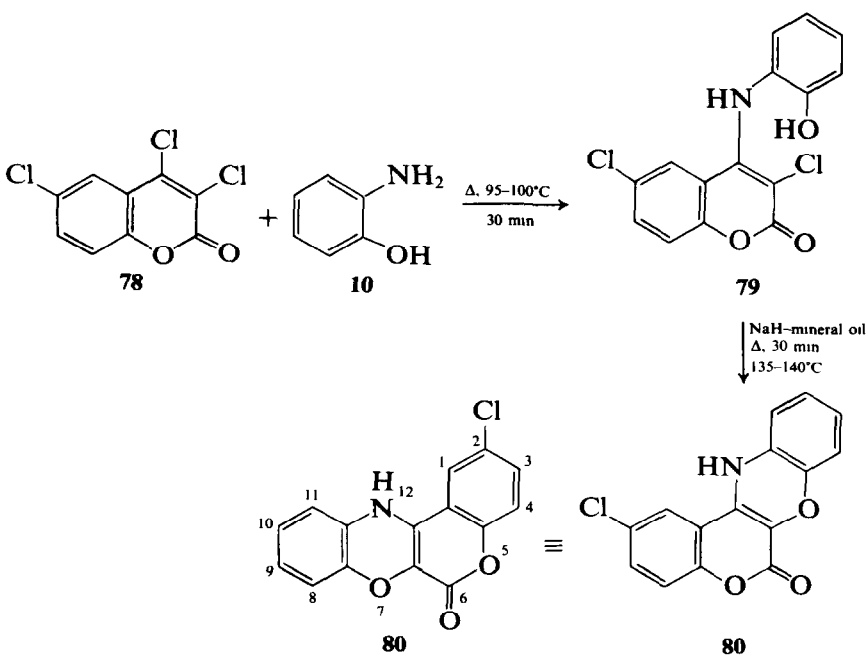
73 23 74

yields.[32] A similar reaction of 3-amino-2-pyridinol (**75**) with compound **23** was unsuccessful due to the low nucleophilic power of the hydroxyl group in compound **75**, which is in equilibrium with the more stable keto form **76**.



75 76 77

Sodium dithionite reduction of compound **74** gave the dihydro-derivative **77**,[32] this compound is unstable to air oxidation and reverts to the quinoid form **74** on exposure to air.



78 10 79

80 80

Benzopyrano[3,4-*b*]benzoxazine

As a variation of the angular phenoxazines, analogues in which one of the ring carbons has been replaced with oxygen have been synthesized. Heating a mixture of 3,4,6-trichlorocoumarin (**78**) and *o*-aminophenol (**10**) in 1-methylpyrrolidine as solvent at 95–99 °C produced an excellent yield of 3,6-dichloro-4-(*o*-aminoanilino)-coumarin (**79**), melting at 241–243 °C. Pyrolysis of compound **79** in 1-methylpyrrolidine in the presence of sodium hydride in mineral oil gave 2-chloro-[1]-benzopyrano[3,4-*b*]benzoxazin-6[12*H*]-one (**80**), melting at 349–352 °C.[33]

3. MISCELLANEOUS ANGULAR PHENOXAZINES

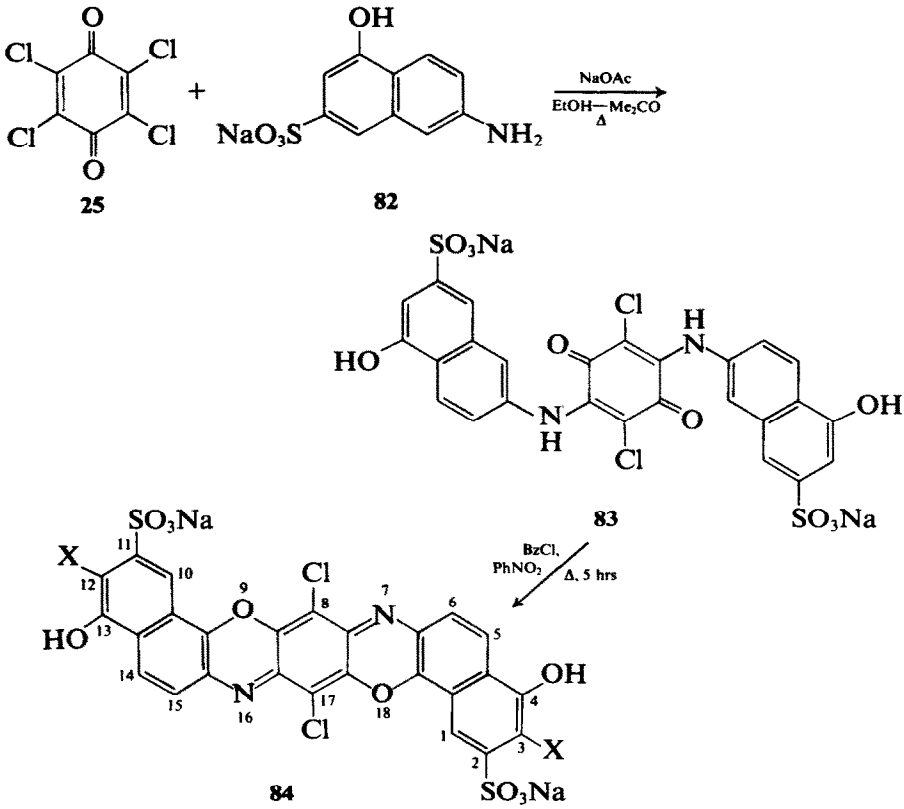
Dibenzo[*c*,*n*]triphenodioxazine

Complex angular phenoxzine dyes have been synthesized. Heating a mixture of chloranil (**25**) and sodium 6-amino-1-naphthol 3-sulphonate (**82**) in ethanol–acetone mixture in the presence of sodium acetate gave the diarylamine **83**, a light brown crystalline powder. Oxidative cyclization in benzoyl chloride in nitrobenzene gave disodium 4,13-dihydroxy-8,17-dichlorodibenzo[*c*,*n*]triphenodioxazine 2,11-disulphonate (**84**; X = H) in 75 % yield.[34] Product **84**, X = H, is a dark blue dye. It is violet–blue in water changing to reddish blue on addition of sodium carbonate and warming slightly. It is a good dye for cotton to which it gives a reddish blue colour on addition of dilute sodium carbonate solution.

The same product, **84**, X = H, is obtained by stirring compound **83** with concentrated H_2SO_4 and MnO_2 for 4 h at room temperature. The tetrasulphonate salt **84**, X = SO_3Na, is obtained by treating compound **83** with chlorosulphonic acid and 25 % oleum on a water bath for 3 h. The latter product, **84**, X = SO_3Na, is a dark purple dye which imparts a purple–blue colour to cotton. Treatment of compound **84**, X = H, with diazotized aromatic amines gave the azo-derivatives. As an example, compound **84**, X = H, diazocouples with benzene diazonium chloride in aqueous sodium carbonate at 0–5 °C to give a blue diazo-dye **84**, X = N=NPh, which is blue in water and bluish green on cotton.[34]

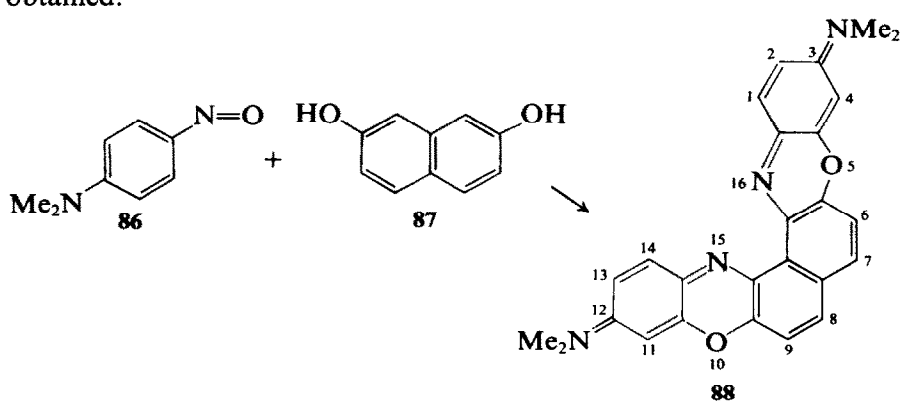
3*H*,12*H*-Phenoxazino[1,2-*a*]phenoxazine

In the course of a study of the theory of colour on the basis of molecular strain, an interesting angular phenothiazine ring system was



25 82 83 84

prepared by Dutt. By heating an alcoholic mixture of *p*-nitrosodimethylaniline hydrochloride (**86**) and 2,7-dihydroxynaphthalene (**87**) for 24 hours, phenoxazino[1,2-*a*]phenoxazine-3,12-bis(dimethylimine) (**88**) was obtained.[35]

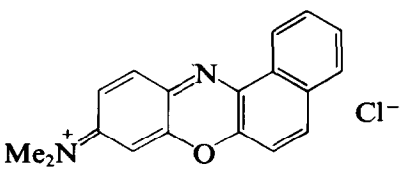


86 87 88

Product **88** is a dark crystalline powder which dissolves in organic solvents giving a dark green coloration.

4. APPLICATIONS

When Meldola[36] pioneered the chemistry of angular phenoxazines in 1879 he was particularly interested in the dyeing properties of these compounds. The beautiful blue colour of one of his products, Meldola Blue (**89**), named after him, induced interest in dyes of this structural type. Meldola Blue can be regarded as the prototype of angular phenoxazines. Equally important dyes of this type are Nile Blue (**90**) and Cresyl Violet (**91**).



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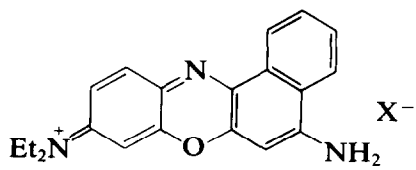

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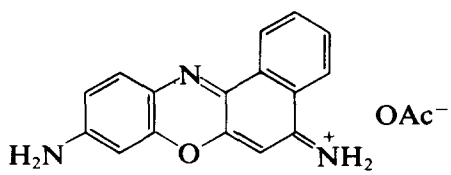


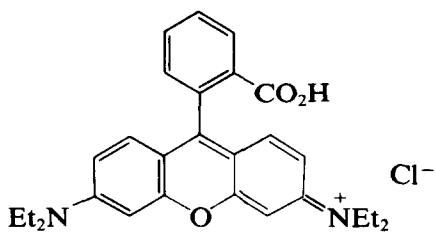
91

The main applications of angular phenoxazines is in the paint, paper and textile industries where they are used as dyes and pigments. Noelting[31] demonstrated the use of the pyrido[3,2-*a*]phenoxazine, **71**, as a mordant blue dye. Muller and Psaar[10] showed that diaminobenzo[*a*]-phenoxazine derivatives of type **17** are useful for dyeing and printing of polyacrylonitrile textiles. Chemists at the American Cyanamid Company[37] produced a series of benzo[*a*]phenoxazine dyes carrying amino functions as in structure **17**. This series of compounds was later shown to be useful as industrial dyes and biological stains. Some of those compounds were also active against certain organisms such as mycobacteria.[37]

In confirmation of Muller's report, the CIBA group[38] pointed out that benzo[*a*]phenoxazine dyes suitable for polyacrylonitrile fibres must have

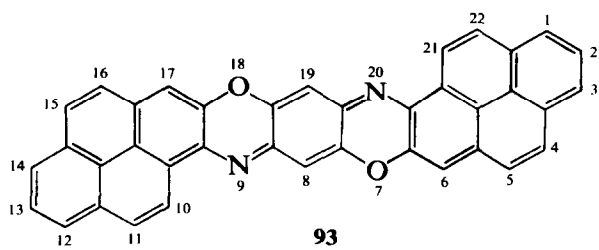
at least one amino group in the 5- or 9-position. Acylation of Nile Blue, **90**, with 4-vinylphthalic anhydride followed by polymerization gave a black dye[39] which is blue in dimethylformamide.

A polychromatic dye[40] suitable for staining tissue was made by refluxing for 2 h a mixture of Nile Blue (**90**) and Rhodamine (**92**). This dye differentially stains biological tissues in varying shades of blue, purple, red, pink and mauve. Both Nile Blue A (**90**, X = hemisulphate) and Cresyl Violet (**91**) acted as saturable dyes for mode-locking of helium–neon lasers.[41]



92

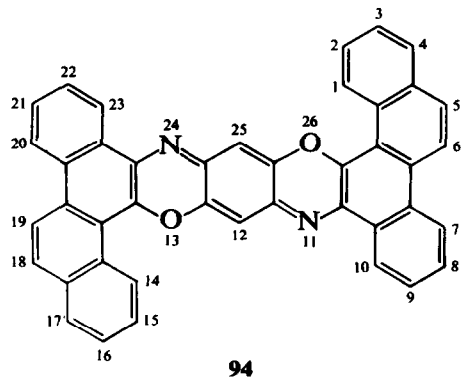
More complex angular phenoxazine derivatives of diphenaleno[1,9-*ab*:1,9-*lm*]triphenodioxazine (**93**) were also prepared.[42] Intensely coloured dyes were obtained from this basic structure. The colours of the derivatives obtained range from red through grey and green to blue and turquoise blue.[43] These dyes are good for dying cotton in neutral baths. Regeneration of the dye *in situ* by first reducing it and then allowing it to oxidize in air gives very fast dyeing.



93

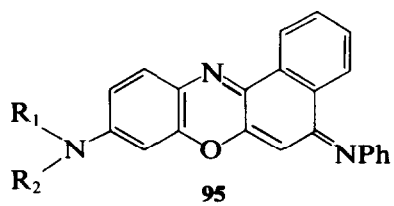
Derivatives of the structurally isomeric dibenzo[*a*,*l*]dinaphtho[2,1-*c*:2,1-*n*]triphenodioxazine (**94**) were also prepared and used as dyes.

It was shown that diazo-systems sensitized by dyes with triplet energies greater than 30 kcal and whose light-activation reaction products can be physically developed, give good metal images. Nile Blue A was found to be a good photosensitizer for this process.[44] It is also a good stain for fats



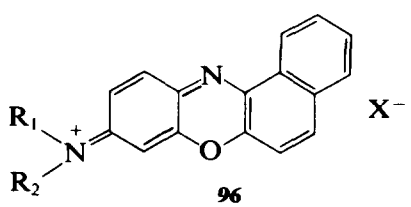
94

for the differentiation of melanins and lipofuscins. Cresyl Violet acetate is a good biological stain for bulk staining of nerve tissues.[45] 5-Phenylimino-9-dialkylaminobenzo[*a*]phenoxazines, **95**, stained fats *in vivo* when given in foods to mice.[46]



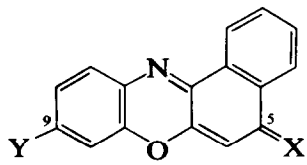
95

Nile Blue A (**90**, X = hemisulphate) and some closely related dyes were found to be useful indicators for titrimetric and equilibrium studies. Nile Blue was found to be the best of those tested.[47] These benzo[*a*]-phenoxazine dyes of type **96** were also used successfully as indicators for determining reduced pyridine coenzymes.[48]



96

The relationship between absorption maxima and luminescence of angular phenoxazine dyes was studied by Stuzka *et al.*[49] They found from this study that the positions *para* to the heterocyclic nitrogen (C-5 and C-9 centres) are the active positions for the absorption and fluorescence properties (structure **97**). Auxochromic substituents in the other positions



97

have only slight influence on the colour and the fluorescence disappears. Decreased fluorescence also results when the substituents in the C-5 or C-9 centre is too large, as in arylamino groups. This substituent at C-5 or C-9 affects the fluorescence if it takes part in the shift of the electrons in the direction of the conjugated system of double bonds of the phenoxazine skeleton and if it is an electron donor but not too bulky.

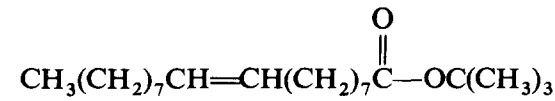
Two angular phenoxazine derivatives, **15** and **16**, suitable as indicators for oxidation–reduction titrations were prepared by Eggers and Dieckmann.[9] The compounds are water-soluble and stable over the whole pH range.

Benzo[*a*]phenoxazine (**2**) and benzo[*c*]phenoxazine (**3**) are retardants[50] in the manufacture of polymethacrylates by the reaction of acetone cyanohydrin or methacrylonitrile and fuming sulphuric acid. The amount of retardant used is roughly 0·003–1 %w/w of the mixture. Antioxidant activity[51] has also been demonstrated for some pyrido[3,2-*a*]phenoxazines (**7**).

Antimony forms 1:1 complexes with Nile Blue A, making Nile Blue a useful material for extraction and photometric determination of antimony.[52] The absorption maximum for the complex in benzene–ethyl acetate is 630 nm and the molar absorptivity is $(7{\cdot}0 \pm 0{\cdot}1) \times 10^4$. The Beer–Lambert Law was observed for 0·05–3·00 ug Sb litre^{-1}. Au(III), Tl(III), Hg(II), Sn(II) and Pb interfere with the determination. Nile Blue A (**90**; X = hemisulphate) is also a good reagent for the extraction and photometric determination of germanium,[53] rhenium,[54] tin[55] and gold.[56] Nile Blue improves the bright colour of copper-plated materials.[57]

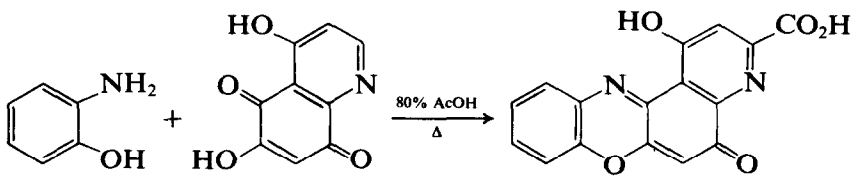
Chemiluminescence studies of oxidation of organic compounds were carried out by Hoefert and Hansmeier.[58] Autoxidation reactions in organic liquids were found to be accompanied by a weak emission of light of about 10^3 quantum cm^{-3} s^{-1}. In model experiments with butyl oleate (**98**), a linear relationship between chemiluminescence intensity and peroxide concentration was found. It was also found that considerable increase in the quantum yield can be achieved by the addition of

benzo[*a*]phenoxazine dyes, due to the energy transmission on the dye structural system.



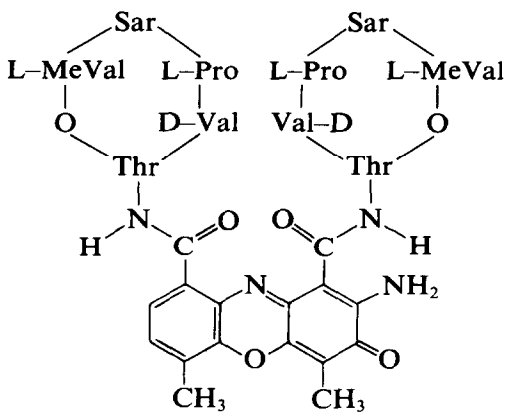
98

A review of the applications of angular phenoxazines cannot be deemed complete without a report on their medicinal properties, for which phenoxazine and phenothiazine are well-known. The antituberculosis effect of benzo[*a*]phenoxazinones was reported by Noda[59] and Funasaki.[60] Catalin (**99**), a pyrido[3,2-*a*]phenoxazinone, is in current use as an anticataract drug.[61] It exhibits high therapeutic activity for cataracts both *in vitro* and *in vivo*. Catalin is prepared by acid-catalysed condensation of *o*-aminophenol with 4,6-dihydroxyquinoline-5,8-dione-2-carboxylic acid (**100**).

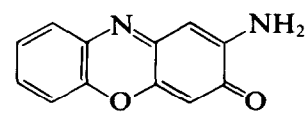


10 **100** **99**

Derivatives of benzo[*a*]phenoxazine also inhibited[62] the growth of some selected species of *Clostridium*. Most marked inhibitory action was however recorded for actinomycin D (**101**) and 2-amino-3*H*-phenoxazin-3-one (**34**). The phenoxazones **101** and **34** are so active that pantothenic



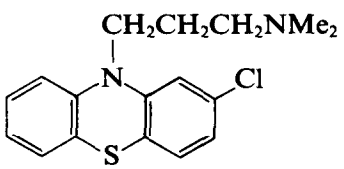
101



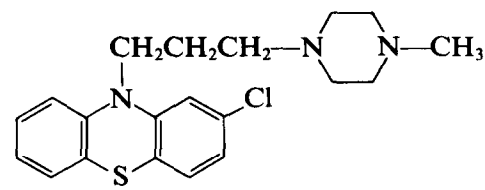
34

acid and β-alanine failed to reverse their inhibitory action on *Clostridium botulinum*.[62]

Although over 240 polycyclic compounds with a wide range of structures were prepared and screened for carcinogenicity,[63] no report has so far been made on the linear angular phenoxazines. Derivatives of the sulphur analogue, phenothiazine, have however been screened. Not only are these compounds non-carcinogenic; two of them, chlorpromazine (**102**) and prochlorperazine (**103**), instead have anticancer activity,[64] a welcome development in the search for the 'magic' anticancer drug.



102



103

Some angular phenothiazines were also found to be non-carcinogenic.[63,65,66] It would have been informative if an assessment of the linear and angular phenoxazine dyes and pigments had been included in a recent interesting survey of some selected dyestuffs and an evaluation of their carcinogenic[67] risks to man. Such detailed studies are needed because of the scanty data on phenoxazines, benzophenoxazines and benzophenothiazines.

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