RECENT ADVANCES IN THE SYNTHESIS OF PHENOTHIAZINES

Sayeed Saraf*, Fatima Al-Omran, and Balkıs Al-Saleh

Department of Chemistry, University of Kuwait, Kuwait

Abstract — This paper reviews the most recent methods for the synthesis of phenothiazine derivatives.

CONTENTS:

I. INTRODUCTION

Phenothiazine and its substituted derivatives are highly reactive compounds; they have aroused the curiosity of chemists and presented many challenges as evidenced by numerous papers published continuously since phenothiazine was first synthesized by Bernthsen[1] in 1883. Advances in the chemistry of the phenothiazines have been reviewed by Massie[2] and Silberg[3]. Since then several new and interesting synthesis of this ring system have been published. The purpose of this review is to classify these, so that gaps may be highlighted with a view to establish new methods.

II. METHODS OF PREPARATION

Broadly speaking, the phenothiazine ring system may be built up using any of the following three methods:

1- The thionation of an appropriately substituted diphenyl amines with sulphur and a catalyst.

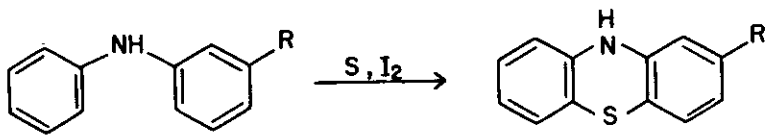
2- The copper-catalysed dehydrohalogenation of substituted 2-amino-2'-halodiphenyl sulphides.

3- The smiles rearrangement of 2-amino-2-nitrodiphenyl sulphides followed by ring closure with the loss of nitrous acid.

We will be discussing the above three methods one by one along with some new routes, which have been recently developed for the preparation of phenothiazine derivatives.

A. THIONATION OF DIPHENYLAMINES

Halogen-containing phenothiazines were synthesised by iodine catalysed thionation of appropriate diphenylamines[4,5]. The course of the thionation was shown to depend on time, temperature, iodine concentration and reaction scale. Thus, thionation of 3-fluoro-3-trifluoromethyldiphenyl amine with sulphur and 3% iodine produced a 12% yield of 2-fluoro-8-trifluoromethylphenothiazine. Using 1% iodine, thionation could not be carried out. Some of the compounds were found to have a tendency to form addition compounds with sulphur. Loss of fluorine during thionation of appropriately substituted diphenylamines was studied and it was observed[6] that it is the presence of fluorine at 2-position rather than the number of fluorine atoms present which affects the ring closure. Thionation method was extended to the preparation of 2-substituted phenothiazines (2) using the appropriate 3-substituted diphenylamines (1). However, the method failed to give 2-methylsulphonyl- and 2-acetoxyphenothiazines[7].

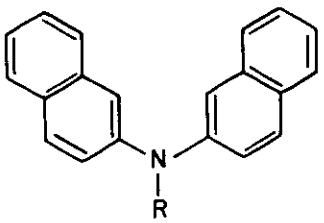


1, R = OH, Bz, SCH_3, SCF_3 2

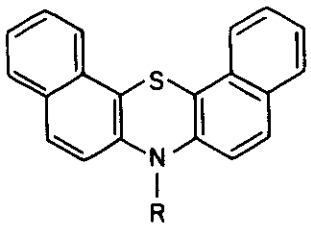
Chandra et al.[8] synthesized 3,7-disubstituted phenothiazines through thionation of the appropriately substituted diphenylamines. During thionation it was observed that heating until the evolution of hydrogen sulphide had ceased completely, or thionation without using any refluxing medium or with anhydrous aluminium chloride in place of iodine, resulted in dehalogenation[9,10]. The yields of phenothiazines were in the range of 30-40%. It has also been reported that thionation of 3-methyl-4-ethyldiphenylamine affords 2-methyl-7-ethylphenothiazine in 61% yield[11].

Extension of thionation method leads to the preparation of dibenzo[c,h]phenothiazine (3). Thus cyclisation of N-methyl-N,N-β,β-dinaphthylamine (4) at 200°C in presence of sulphur and traces of iodine afforded 3 and none of 5. Treatment

of 3 with potassium in toluene followed by the addition of methyl iodide gave 5



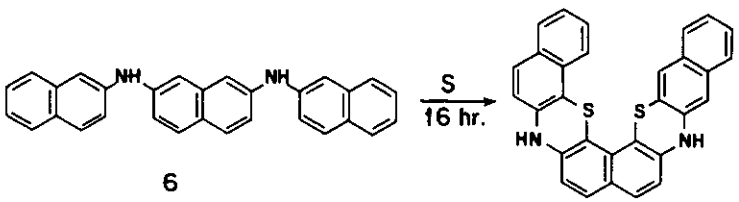
4, R = CH_3



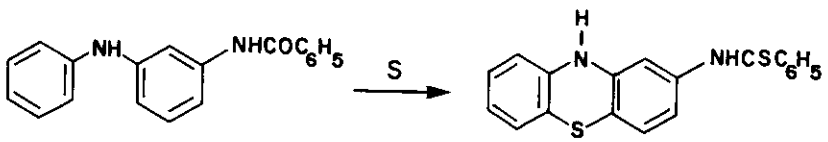
3, R = H
5, R = CH_3

in 43% yield[12].

Similarly ring closure of 2,7-bis-β-naphthylaminohaphthalene (6) in boiling trichlorobenzene in presence of sulphur gave phenothiazinophenothiazine (7) in 35% yield[13].



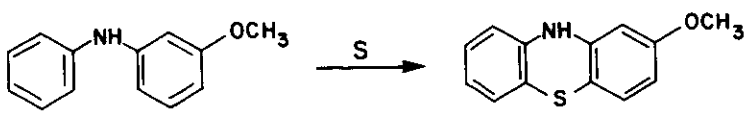
6 7



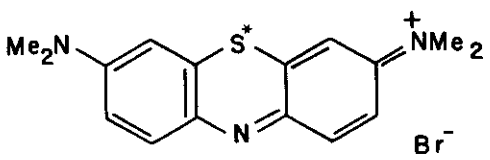
8 9

Using the same method, 2-phenylthioacylaminophenothiazine (9) was prepared by heating m-benzoylaminodiphenylamine (8) with sulphur in 63% yield[14]. Similarly, 2-methoxyphenothiazine was prepared in 90% yield by heating m-methoxydiphenylamine with sulphur using decaline as solvent at 150-155°C for 6-7 h.[15]

Thionation method has been used on an industrial scale for the preparation of

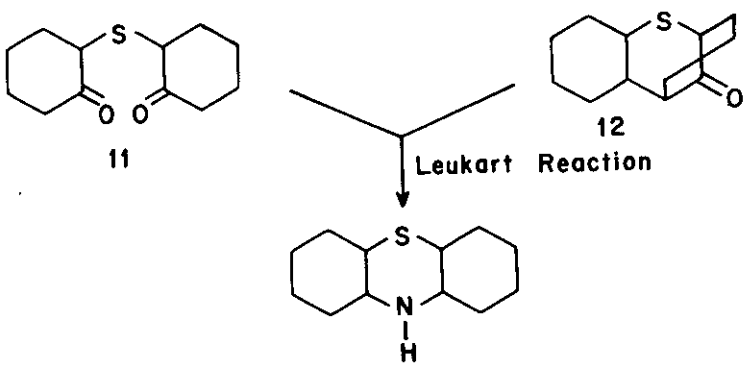


phenothiazine[16]. The method involves heating diphenylamine (140 parts), sulphur (8 parts) and iodine (0.62 parts) at 180-190°C for 1 h. The crude product after treatment with an equal volume of methanol for 40 min. at 65°C followed by cooling and crystallisation from methanol afforded phenothiazine in 75% yield. The same procedure was used for the preparation of methylene blue labelled with ^{36}S. Diphenylamine and ^{36}S were melted together to give the labelled phenothiazine. Bromination followed by treatment with dimethylamine gave methylene blue (10) in 20% yield with radiochemical purity of 92%[17].



10

Reaction of 2-chlorocyclohexanone with sodium sulphide at 150°C in 50% methanol gave 2,2-thiodicyclohexanone (11) in 41% yield, whereas at room temperature for 2 days 12 was isolated. Leukart reaction of 11 and 12 gave perhydrophenothia-

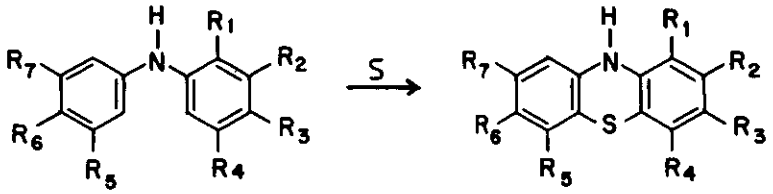


11 12

13

zine (13)[18]. The results of thionation are given in Table I.

Table I.



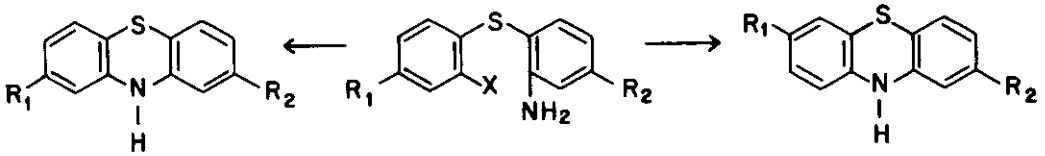
R_1	R_2	R_3	R_4	R_5	R_6	R_7	yield %	Ref.
H	F	H	H	CF_3	H	H	12	4
Cl	H	H	H	H	H	H	43	4
H	CH_3	H	H	CF_3	H	H	18	4
OCH_3	H	H	H	CF_3	H	H		
H	CF_3	H	H	H	H	H	4	5
H	CF_3	H	H	H	H	CH_3	52	5
F	H	H	H	H	H	H	9.3[a]	6
H	F	H	H	H	H	H	52	6
H	F	H	F	H	F	H	20	6
H	F	H	F	F	H	F	20	6
H	H	CF_3	H	H	H	H	52	6
H	OH	H	H	H	H	H	11	7
H	SCH_3	H	H	H	H	H	43	7
H	SCF_3	H	H	H	H	H	45[b]	7
H	SO_2CH_3	H	H	H	H	H	77	7
H	SO_2CF_3	H	H	H	H	H	60	7
H	H	OC_2H_5	H	H	OC_2H_5	H	40	8
H	H	OC_2H_5	H	H	OCH_3	H	38	8
H	H	Cl	H	H	OC_2H_5	H	30	8
H	H	Br	H	H	OCH_3	H	30	8
H	H	Br	H	H	OC_2H_5	H	35	8
H	H	Br	H	H	Cl	H	30	8
H	CH_3	H	H	H	H	H		19
H	H	C_8H_{17}	H	H	C_8H_{17}	H	50	20

a. Phenothiazine was also isolated in 1.4%

b. From mother liquor 2% of 4-trifluoromethylmercaptophenothiazine was also isolated.

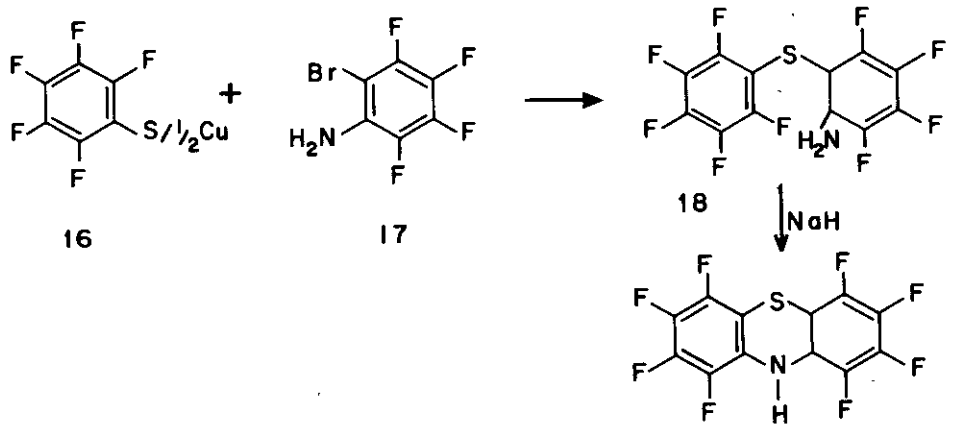
B. CYCLISATION OF DIPHENYL SULPHIDES

The synthesis of phenothiazines starting with o-amino-o-halogenodiphenyl sulphides could result in either an Ullmann-type cyclisation to yield 2,8-disubstituted phenothiazines (14) or through a smiles rearrangement, may afford 2,7-disubstituted phenothiazines (15).



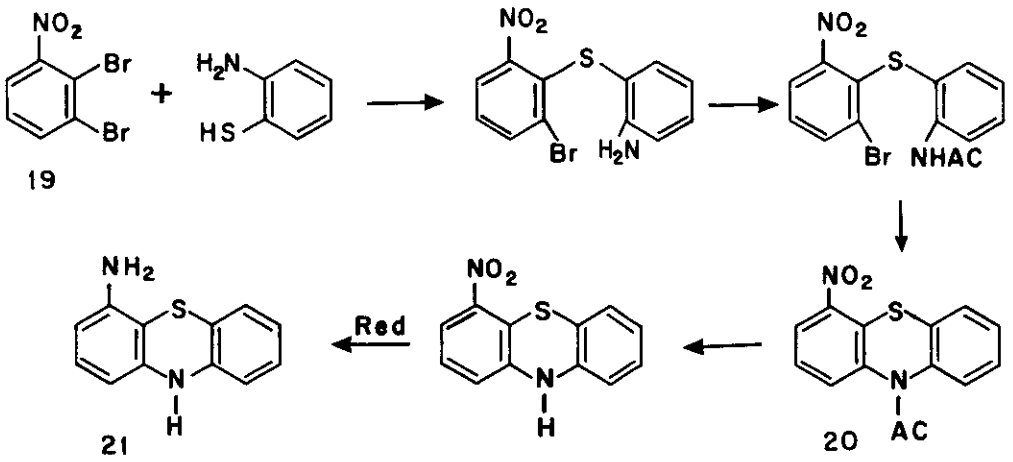
14 15

Fluorinated phenothiazines have been synthesised by adding cuprous pentafluorophenolate (16) to 2-bromotetrafluoroaniline (17) to give 2-aminomonofluorodiphenyl sulphide (18). Reductive cyclisation of 18 with sodium hydride gave the corresponding polyfluorinated phenothiazines[21]. In another method the fluorohydrocarbon and 2-aminothiophenol on refluxing in dimethylformamide for 5.5 h. under nitrogen gave the corresponding fluorinated hydrocarbon[22].

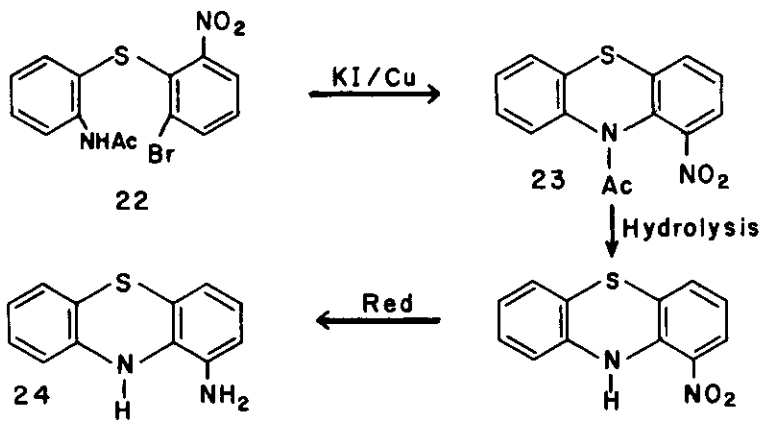


16 17 18

This reaction has been used successfully in the cyclisation of o-nitrodiphenyl-sulphide to phenothiazine using triethyl phosphite as cyclising agent. In a

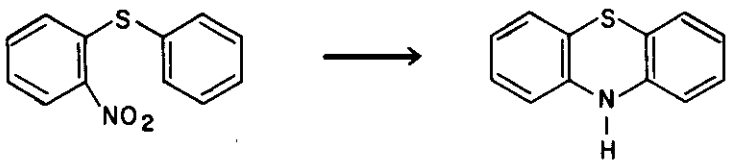


similar reaction, 2,3-dibromonitrobenzene (19) with o-aminothiophenol gave 92% of the corresponding diphenyl sulphide[23]. Acetylation followed by cyclisation with Cu/K_2CO_3 gave 50% of (20), which on hydrolysis gave nitrophenothiazine. Reduction with hydrazine hydrate gave 75% of the aminophenothiazine[24] (21).



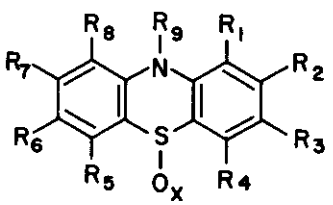
Heating 22 in nitrobenzene with potassium iodide and copper afforded 23 in 60% yield. Hydrolysis of 23 followed by reduction gave the amine (24) in 65% yield[25].

Triethylphosphite has also been used as cyclising agent in the preparation of substituted or unsubstituted phenothiazines. Thus cyclisation of diphenyl-sulphide(25) with triethyl phosphite gave the corresponding phenothiazine(26)[27]. Results are summarized in Table 2.



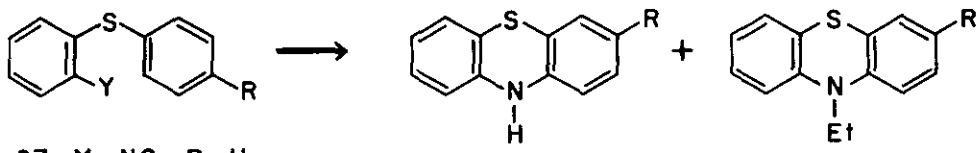
25 26

Table 2



R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	X	Ref.
F	CH_3	F	F	H	H	H	H	H	O	21
F	CH_3	F	F	F	F	F	H	H	O	21
F	CF_3	F	F	H	H	H	H	H	O	21
F	F	F	F	H	H	H	H	H	O	21
F	F	F	F	H	F	F	F	H	O	21
F	F	F	F	H	H	CH_3	H	H	O	21
F	CF_3	F	F	H	H	H	H	$C_3H_6NMe_2$	O	21
F	F	F	F	F	F	F	F	$C_3H_6NMe_2$	1	22
F	CF_3	F	F	F	F	F	F	$C_3H_6NMe_2$	O	22
F	CF_3	F	F	H	H	H	H	$C_3H_6NMe_2$	O	22
F	H	F	F	F	F	F	F	$C_3H_6NMe_2$	O	22
F	H	F	F	H	H	H	H	$C_3H_6NMe_2$	O	22
H	F	H	H	F	F	F	F	$C_3H_6NMe_2$	O	22
H	H	H	H	F	F	F	F	$C_3H_6NMe_2$	O	22
F	CF_3	F	F	H	H	H	H	$C_3H_6NMe_2$	1	22
F	CF_3	F	F	H	H	H	H	C_3H_6X	O	22
NO_2	H	NO_2	H	H	H	F			O	26
NO_2	H	Cl	H	H	H	F	H		O	26
NO_2	H					F	H		O	26
NO_2	H	NO_2	H	H	H	F	H		1	26
NO_2	H	Cl	H	H	H	F	H		1	26
NO_2	H	F	H	H	H	F	H		1	26

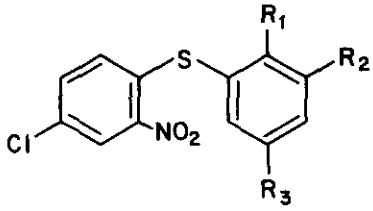
Cadogan et al.[28] observed that in the cyclisation of phenyl-2-nitrophenyl sulphide (27) with triethyl phosphite, 10-ethylphenothiazine is also formed, although in low yield. This was shown to be formed by ethylation of the first phenothiazine by triethyl phosphite. In case of 4-methylphenyl-2-nitrophenyl sulphide (28), a new molecular rearrangement occurred and instead of isolating 2-methylphenothiazine, 3-methylphenothiazine and a trace of 10-ethyl-3-methyl-phenothiazine were isolated. Using purified deperoxidised cumene as a solvent, the yield of phenothiazine was considerably increased and the yield of



27, Y = NO_2, R = H

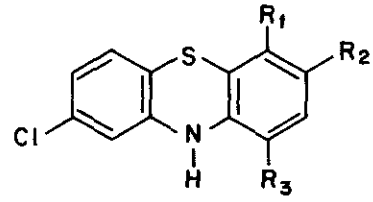
28, y = NO_2, R = CH_3

N-ethylated side products reduced. In a similar reaction, 4'-chloro-2,5-dimethoxy-2'-nitrodiphenyl sulphide (29) gave not only 2-chloro-6,9-dimethoxyphenothiazine (30) but also 2-chloro-7,9-dimethoxyphenothiazine (31). On the other hand cyclisation of 4'-chloro-3,5-dimethoxy-2'-nitrodiphenyl sulphide (32) failed to give 2-chloro-6,8-dimethoxyphenothiazine. Instead, 2-chloro-7,9-dimethoxy isomer (31) was obtained as the sole product. This has been attributed to the strong ortho and para directive effects of the two methoxyl groups on the available 2 and 5 positions[29]



29, $R_1 = R_3 = OCH_3$; $R_2 = H$

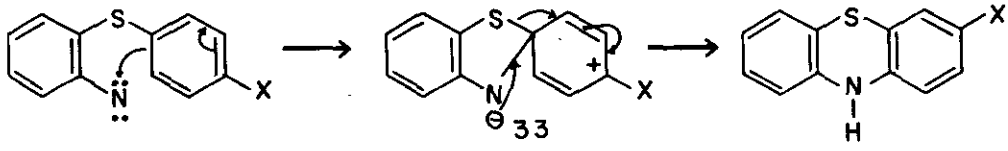
32, $R_2 = R_3 = OCH_3$; $R_1 = H$



30, $R_1 = R_3 = OCH_3$; $R_2 = H$

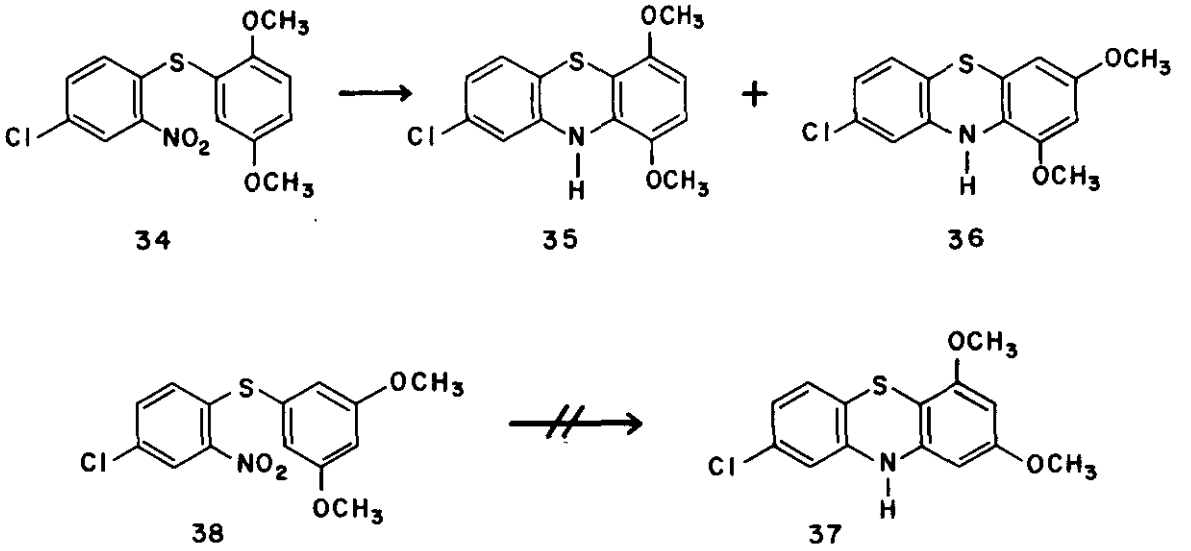
31, $R_2 = R_3 = OCH_3$; $R_1 = H$

As regards mechanism of the reaction, a triplet nitrene intermediate was proposed. Attack at position 1 gives the spiro-diene intermediate (33). Sigmatropic followed by prototropic shift then gives the rearranged 3-substituted phenothiazine.



The initial cyclisation conforms to the general pattern of cyclisation observed previously[28,30] in that, a five membered heterocyclic ring containing nitrogen is first formed before rearrangement to the six-membered ring.

Cyclisation of 4'-chloro-2,5-dimethoxy-2'-nitrodiphenyl sulphide (34) with triethylphosphite gave 35 and an unexpected minor product, 2-chloro-7,9-dimethoxyphenothiazine (36)[31]. Cyclisation of 38 failed to yield (37), but instead gave 36 as the sole phenothiazine derivative.

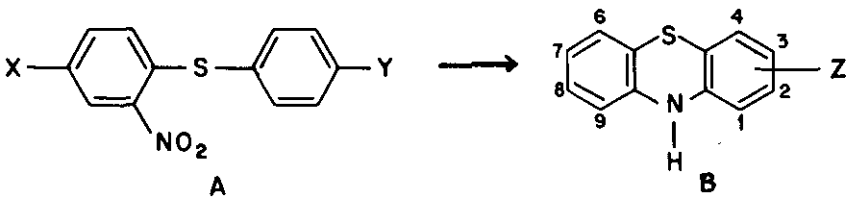


34 35 36

38 37

The results are summarised in Table 3.

Table 3

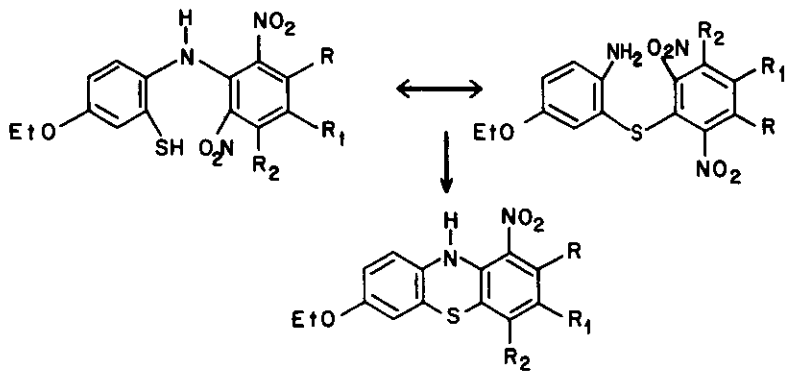


A		B		
X	Y	Z	yield %	Ref.
Cl	H	2-Cl	55	28
H	Cl	3-Cl	58	28
H	Bu^t	3-Bu^t	74	28
H	OCH_3	3-OCH_3	85	28
CH_3	H	2-CH_3	52	28
H	CH_3	3-CH_3	56	28
$COOC_2H_5$	Bu^t	3-Bu^t,8-$COOC_2H_5$	54	28
H	Bu^t	3-Bu^t	55	28
H	H	H	54	28
CH_3	H	2-CH_3	50	28
H	2_H*	3-^2H*	60	28

• Incorporation 90%

C. SMILES REARRANGEMENT

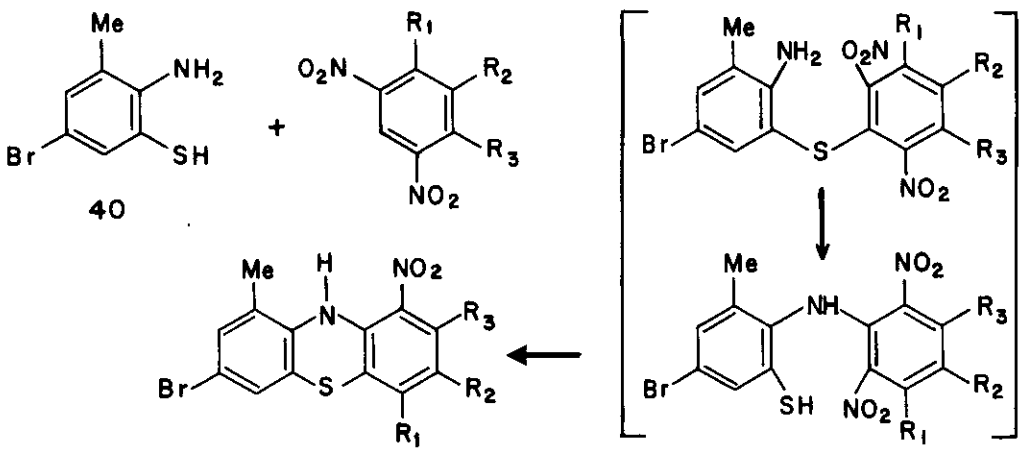
Although a number of methods have been developed for the synthesis of nitrophenothiazines, none have been found convenient for direct synthesis of nitrophenothiazines. Preparation of nitrophenothiazines by thionation of nitrophenylamines have already been reported unsuccessful[32] and preparation by nitration of phenothiazines is invariably accompanied by simultaneous oxidation of 5-sulphoxides[33] and the sulphoxides obtained are to be reduced to get nitrophenothiazines. A direct method for the synthesis of nitrophenothiazines via smiles rearrangement, which occurs in situ, involves the generation of o-aminothiophenol by hydrolytic cleavage of 2-aminobenzothiazole with 50% potassium hydroxide solution, followed by condensation with reactive halogenonitrobenzenes in alcoholic sodium hydroxide. Gupta[34] used the procedure successfully in the preparation of 7-ethoxyphenothiazines (39).



$R = R_2 = H$, $R = NO_2$
$R = R = H$, $R_1 = Cl$
$R_1 = H$, $R_2 = R = Br$

39

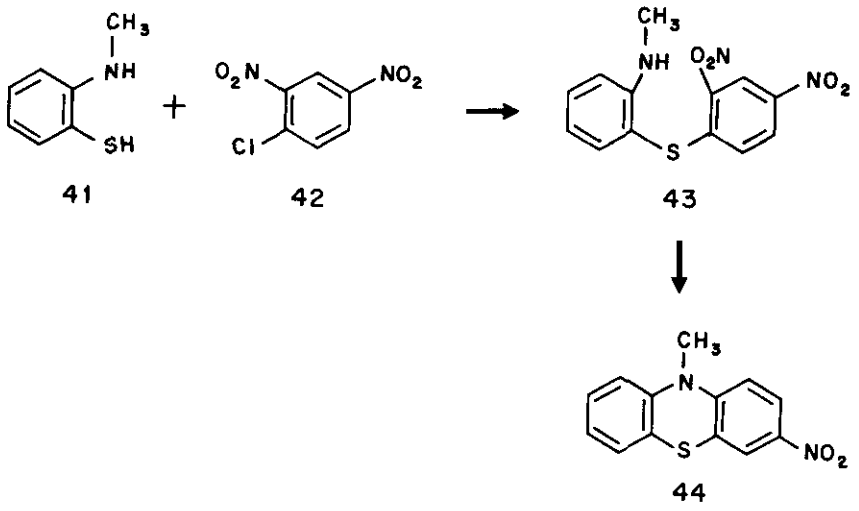
Unsubstituted nitrophenothiazines have also been synthesised from 2-amino-3-methyl-5-bromothiol (40), which in turn was obtained from Herz compound[35]. The thiophenol (40) was converted to 1-nitro-9-methylphenothiazine by treatment with a halogenonitrobenzene via smiles rearrangement. The major advantage of this reaction would be to prepare phenothiazines with a novel type substitution,



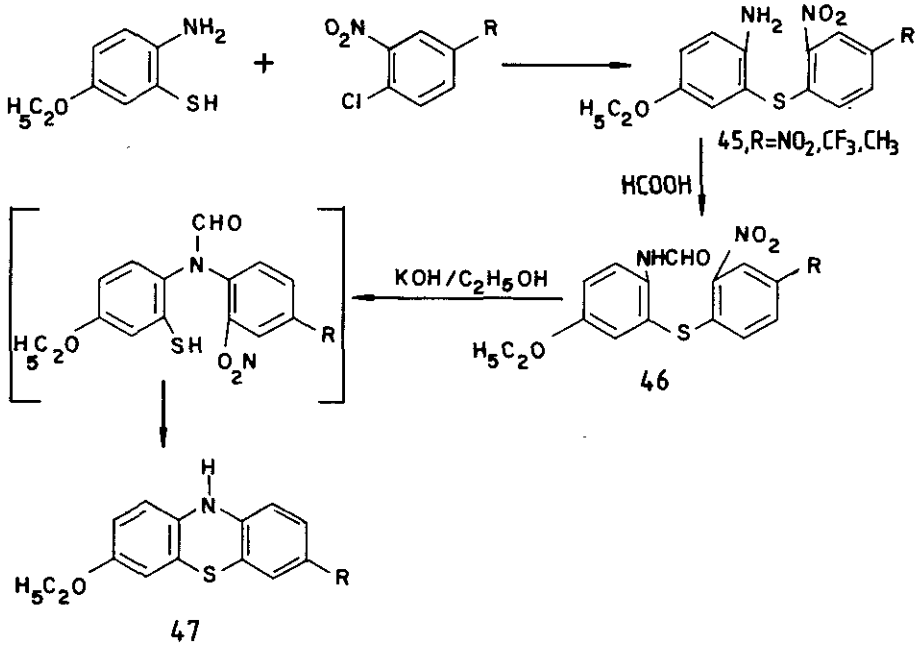
40

which is otherwise accessible with difficulty[36].

Synthesis of 3-nitro-10-methylphenothiazine was carried out by condensing o-methylaminothiophenol (41) with 2,4-dinitrochlorobenzene (42). The 2,4-dinitrodiphenylsulphide (43), thus obtained was cyclised via the smiles

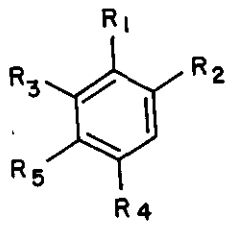


rearrangement[37] to (44) in 88% yield[38]. It may be mentioned here that compound 44 could not be obtained by direct nitration of 10-methylphenothiazine, as the nitration is always accompanied by oxidation at the level of the sulphur bridge leading to 5-oxides or even to 5,5-dioxides[39-41]. 3-Ethoxy-7-substituted phenothiazines were also prepared by smiles rearrangement. Thus condensation of 2-amino-5-ethoxythiophenol with substituted 2-chloronitrobenzenes afforded the corresponding diphenyl sulphides (45), which on treatment with formic acid gave the corresponding formamido derivative (46). Treatment of 46 with alcoholic potassium hydroxide afforded the isolated phenothiazine (47)[42].



Sharma et al.[43] have observed the formation of nitrophenothiazines did not take place unless both the positions ortho to the activated halogen atom in halogenonitrobenzenes are substituted either by the two nitro groups or by one nitro and one halogen. In the latter case, where the reactive halogen atom has a nitro as well as a halogen atom in both of its ortho positions, the cyclisation always took place by the elimination of the halogen atoms in preference to the nitro group. According to the authors[43], 1-chloro-, 2,4-dinitro-, 1-chloro-5-methyl-2,4-dinitro- and 1,4-dichloro-2-nitrobenzene, which had only one nitro group *ortho to the activated halogen atom provided* 2-amino-2',4'-dinitro-2',4'-dinitro-5-methyl-, and 2-amino-4'-chloro-2'-nitrodiphenyl sulphide but no phenothiazine. Halogenonitrobenzenes, which are unsymmetrically substituted and possess two nitro groups ortho to the activated halogen atom yielded two isomeric phenothiazines, as in case of 1-chloro-2,4,6-trinitro-5-methylbenzene, the two isomers namely 1,3-dinitro-2-methylphenothiazine (15%) and 1,3-dinitro-4-methylphenothiazine (75%) were isolated.

This instantaneous dual process of smiles rearrangement and ring closure has been attributed to the increased resonance effect due to the presence of the two nitro groups at both the ortho positions as the halogenonitrobenzenes (48-51) and the combined resonance and inductive mechanisms enforced by the one nitro and one halogen atom as in halonitrobenzene such as in 52-55.



48, $R_2 = R_3 = NO_2$, $R_1 = Cl$, $R_4 = R_5 = H$

49, $R_2 = R_4 = R_3 = NO_2$, $R_1 = Cl$, $R_5 = H$

50, $R_2 = R_3 = NO_2$, $R_1 = R_4 = Cl$, $R_5 = H$

51, $R_2 = R_3 = R_4 = NO_2$, $R_1 = Cl$, $R_5 = CH_3$

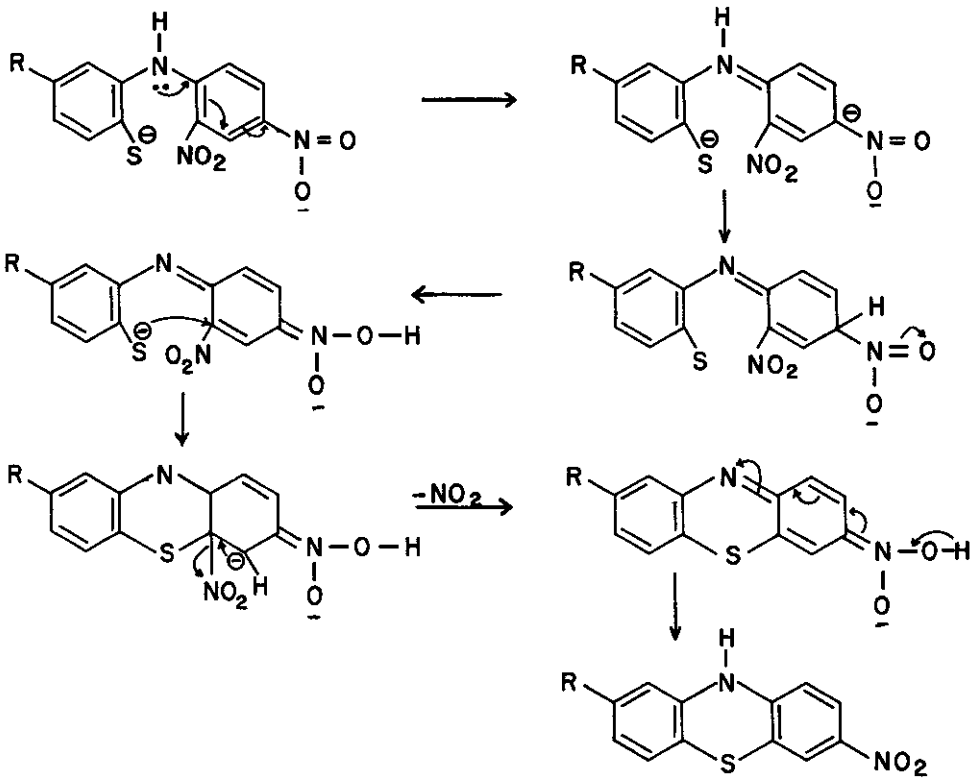
52, $R_1 = R_2 = Cl$, $R_3 = R_4 = NO_2$, $R_5 = H$

53, $R_1 = Cl$, $R_2 = Br$, $R_3 = R_4 = NO_2$, $R_5 = H$

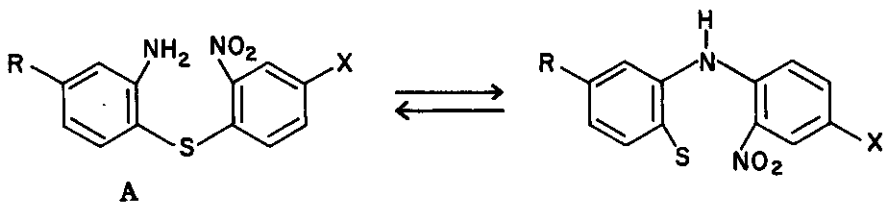
54, $R_1 = Cl$, $R_2 = I$, $R_3 = R_4 = NO_2$, $R_5 = H$

55, $R_1 = Br$, $R_2 = Cl$, $R_3 = R_4 = NO_2$, $R_5 = CH_3$

Chaudhary[44] has suggested the following mechanism for the nitro group induced smiles rearrangement.



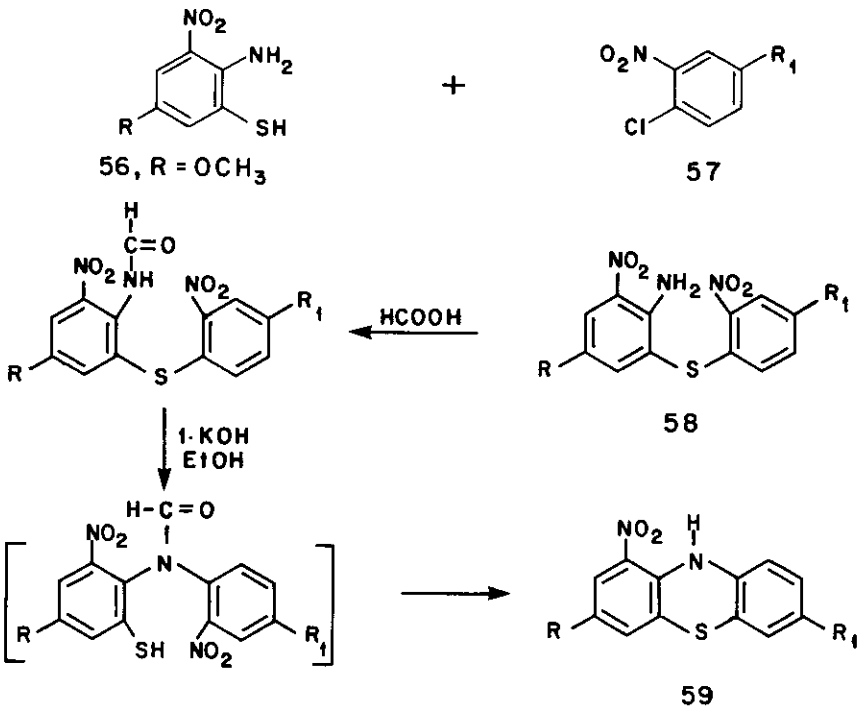
The intermediate A formed in the reaction existed in the tautomeric form and it



A

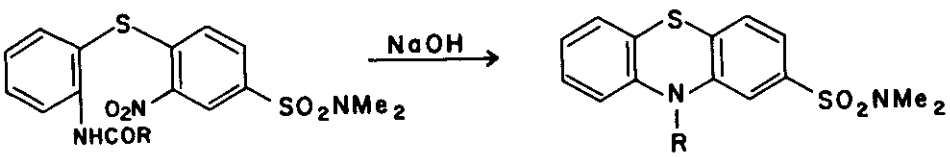
involves the removal of a proton from 10-N (NH), away from 2-nitro group, the hydrogen bonding between this proton and 2-nitro group becomes improbable. This particular disposition of 4-nitro group with respect to NH-, resulting in the double bond character between C and 10-N linkage, which might be fixing up the spatial geometry of the 2-nitro group with respect to mercaptide ion, thereby facilitating the ring closure.

Smiles rearrangement has also been used in the preparation of 3-alkoxy-1-nitro-7-substituted phenothiazines[45]. Thus, condensation of 5-alkoxy-2-amino-3-nitrothiophenol (56) with substituted o-chloronitrobenzenes (57) afforded 5-alkoxy-2-amino-2',3-dinitro-4'-substituted diphenyl sulphides (58). Heating (58) with formic acid gave the corresponding formyl derivatives, which on treatment with alcoholic potassium hydroxide afforded 3-alkoxy-1-nitro-7-substituted phenothiazines (59).



Extension of this method leads to the preparation of 3-mono- and 3,7-di-substituted phenothiazine[46]. The major intermediate in the synthesis, namely, o-aminothiolphenol, was prepared through hydrolytic cleavage of substituted 2-aminobenzothiazoles in good yield, although number of other methods are reported in the literature, but most of them are, however, ambiguous, and in some case the products were not properly characterised[47-55]. Condensation of 2-aminothiophenol with halogenonitrobenzene followed by refluxing the diphenyl sulphide with formic acid resulted in the formation of substituted formamidodiphenyl sulphides, which on cyclisation gave the corresponding phenothiazines. The results are summarised in Table 4.

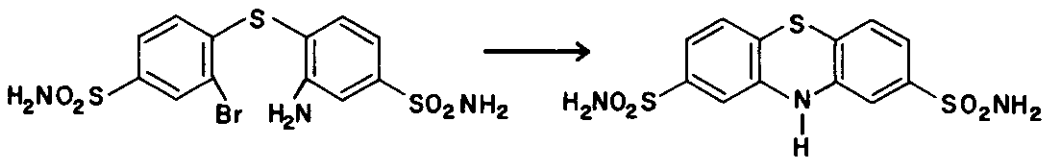
Benzenesulfonamide (59a) was obtained in 88% yield by acylation of the corresponding amino derivatives. Cyclisation with sodium hydroxide in ethanol



59a, R = H, CH_3 59b, R = H

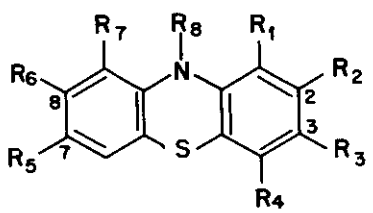
gave 75% phenothiazine sulfonamide (59b)[53].

On the other hand, 2,8-disulfamoyl phenothiazine (59c) was isolated by intramolecular cyclisation of (59d) in dimethyl formamide in the presence of Cu/K_2CO_3[54].



59d 59c

Table 4

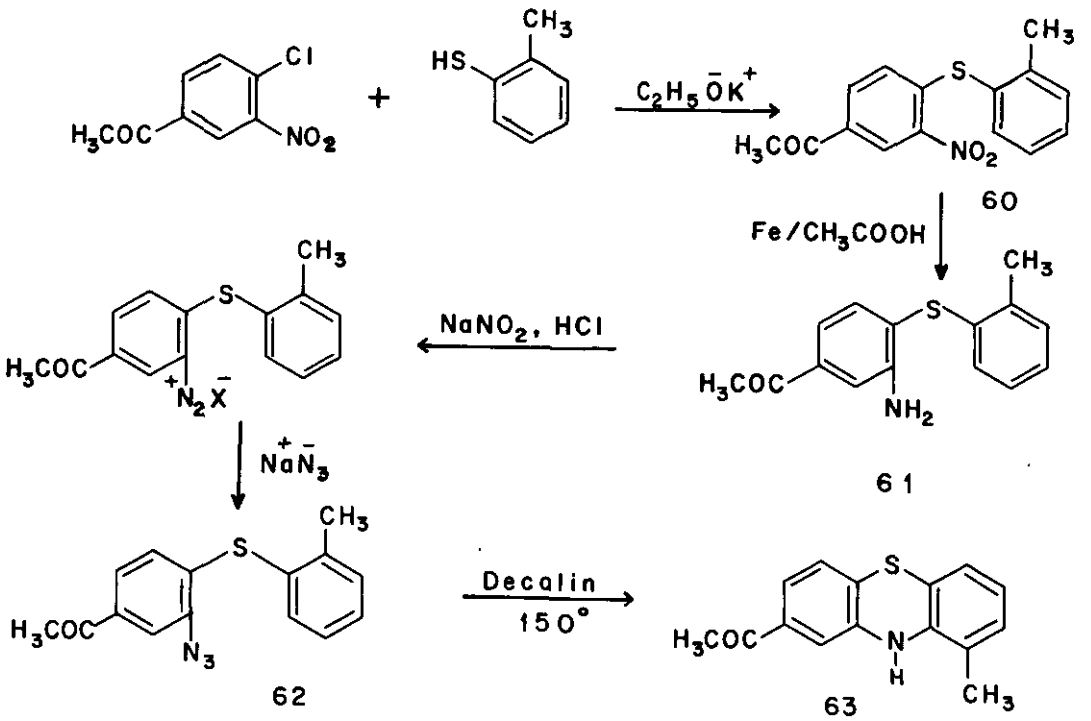


R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	yield	Ref.
NO_2	H	NO_2	H	OC_2H_5	H	H	H	80	34
NO_2	H	Cl	H	OC_2H_5	H	H	H	75	34
NO_2	Br	H	Br	OC_2H_5	H	H	H	80	34
NO_2	H	NO_2	H	Br	H	CH_3	H	50	36
NO_2	H	Cl	H	Br	H	CH_3	H	53	36
NO_2	Br	H	Br	Br	H	CH_3	H	50	36
NO_2	H	H	H	H	H	H	H	68	43
NO_2	H	NO_2	H	H	H	H	H	95	43
NO_2	H	Cl	H	H	H	H	H	90	43
NO_2	CH_3	NO_2	H	H	H	H	H	15	43
NO_2	H	NO_2	CH_3	H	H	H	H	75	45
H	H	NO_2	H	OC_2H_5	H	H	H	-	42
H	H	CH_3	H	OC_2H_5	H	H	H	-	42
H	H	CF_3	H	OC_2H_5	H	H	H	-	42
H	Cl	H	H	NO_2	H	H	H	55	44
H	Br	H	H	NO_2	H	H	H	60	44
H	CH_3	H	H	NO_2	H	H	H	67	44
H	OCH_3	H	H	NO_2	H	H	H	45	44
H	OC_2H_5	H	H	NO_2	H	H	H	36	44
H	CF_3	H	H	NO_2	H	H	H	45	44
H	NO_2	H	H	NO_2	H	H	H	26	44
H	CH_3	H	H	CH_3	H	H	H	65	44
H	CH_3	H	H	OCH_3	H	H	H	50	44
H	CH_3	H	H	Br	H	H	H	30	44
H	CH_3	H	H	Cl	H	H	H	35	44
NO_2	H	OCH_3	H	NO_2	H	H	H	52	45
NO_2	H	OCH_3	H	Cl	H	H	H	60	45
NO_2	H	OCH_3	H	CH_3	H	H	H	65	45
NO_2	H	OC_2H_5	H	NO_2	H	H	H	52	45
NO_2	H	OC_2H_5	H	Cl	H	H	H	50	45
NO_2	H	OC_2H_5	H	CH_3	H	H	H	60	45
H	H	OCH_3	H	H	H	H	H	30	46

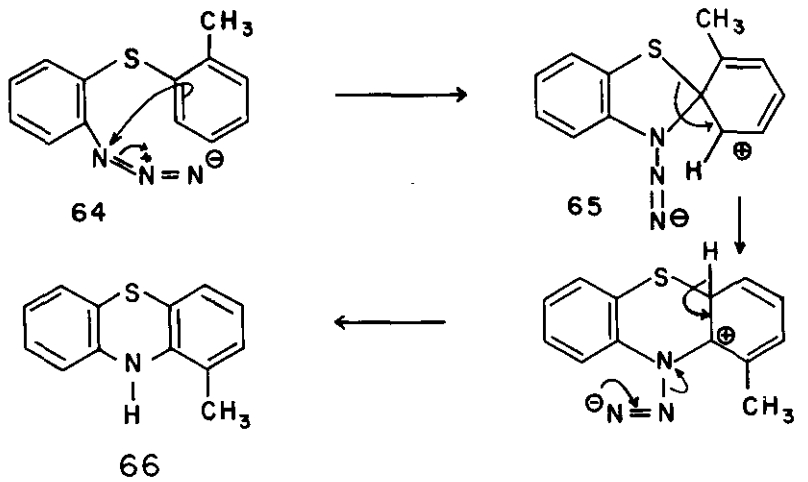
R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	yield	Ref.
H	H	OC_2H_5	H	H	H	H	H	26.4	46
H	H	OCH_3	H	Cl	H	H	H	43.6	46
H	H	OC_2H_5	H	Cl	H	H	H	40	46
H	H	Br	H	Cl	H	H	H	46	
H	H	NO_2	H	H	H	H	H	46	46
H	H	NO_2	H	NO_2	H	H	H	55	46
H	H	NO_2	H	Cl	H	H	H	23	46
H	H	NO_2	H	H	H	H	H	-	52
H	H	Br	H	Cl	H	H	H	-	52
H	H	Cl	H	NO_2	H	H	H	-	52
H	H	H	H	Br	H	H	H	-	52
H	CF_3	H	H	SO_2NH_2	H	H	Ac	-	55
H	H	Cl	H	SO_2NH_2	H	H	Ac	-	55
H	Cl	H	H	SO_2NH_2	H	H	Ac	91	55
H	H	CF_3	H	H	SO_2NH_2	H	H	-	55
NO_2	H	NO_2	H	H	H	H	H	-	55
NO_2	NO_2	H	NO_2	H	H	H	H	-	56
H	OCH_3	H	H	NO_2	H	H	H	90	57
H	OC_2H_5	H	H	NO_2	H	H	H	85	57
H	CH_3	H	H	NO_2	H	H	H	95	57
H	Cl	H	H	NO_2	H	H	H	93	57

D. FROM AZIDES

In the cyclisation of 2-azidodiphenyl sulphides into phenothiazine derivatives, a new type of rearrangement has been shown to occur[58]. Treatment of thiocresol with 3-nitro-4-chloroacetophenone gave 2-nitro-4-acetyl-2'-methyldiphenyl sulphide (60), which on reduction with iron and acetic acid afforded the amine (61). Diazotization followed by treatment with sodium azide affords 62, which on heating in decaline at 150°C afforded the corresponding phenothiazine (63).

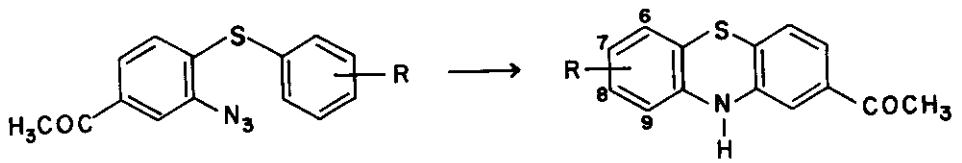


The proposed mechanism for the formation of phenothiazine involves the azide (64) as an intermediate. Attack on N^+ by the double bond of the 2nd ring gives



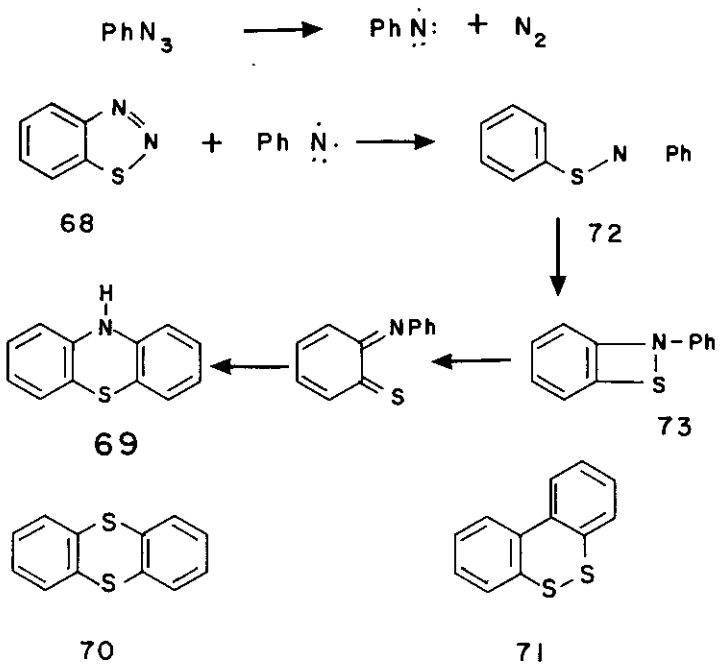
(65) as an intermediate. Migration of C-5 bond at C-1 followed by loss of proton affords 66.

It has been observed that if R is in the 2'-position, the phenothiazine 67 contains R at 9-position. Similarly, when R is at 4'-position, a compound in which R is at 7 position is obtained. The results are summarised in Table 5.



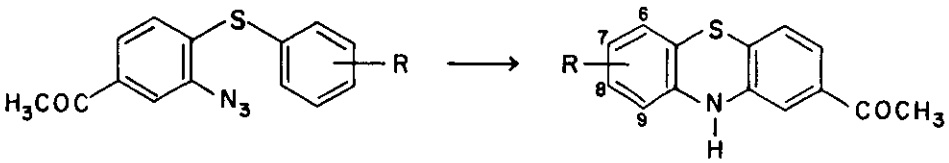
67

Thermolysis of phenyl azide in the presence of 2 or 5 mol equivalent of benzothiadiazole (68) at 153°C for 7 h led to the formation of phenothiazine (69), thianthrene (70) and dibenzo[c,e]-o-dithiin (71)[59]. The formation of 69 was rationalized by invoking an initial attack by a triplet nitrene on the sulphur of 68 and formation after nitrogen loss of a diradical intermediate (72). Formation of 73 by 1,4-cyclisation leads to the formation of 69 by valence



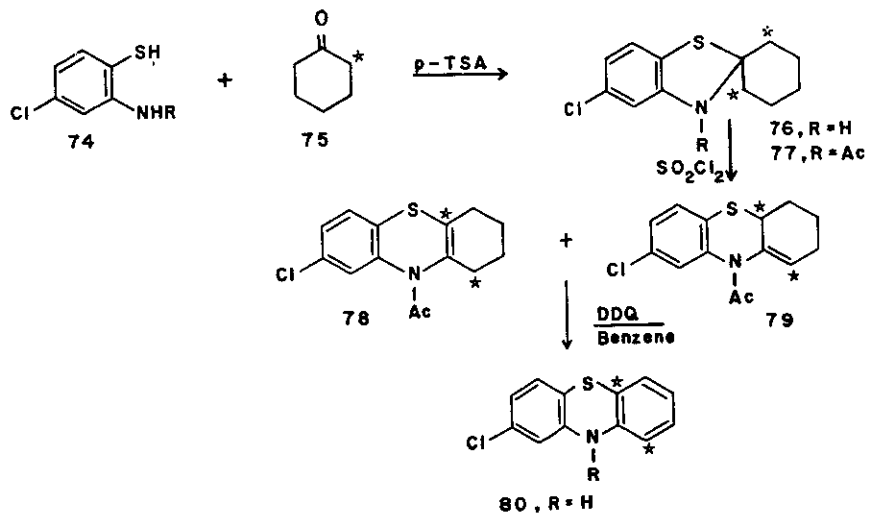
isomerisation followed by electrocyclic closure and aromatization.

Table 5



R	Original position of R	Final position or R	Yield %	Ref.
OCH_3	2'	9	58	58
OCH_3	3'	8	5	
OCH_3	4'	7	50	
CH_3	2'	9	52	
CH_3	3'	6	5.5	
CH_3	4'	7	26	
CH_3S	4'	7	40	
Cl	2'	9	6	
Cl	4'	7	3	

Ring labelled (^{14}C or ^{13}C) 2-substituted phenothiazines were prepared for the first time by Muccino et al[60] utlizing reported ring expansion reaction[61]. Condensation of 2-amino-4-chlorothiophenol (74) with cyclohexanone-2 ^{14}C[62] (75) afforded spiro 2,3-dihydro-1,3-benzothiazole (76). Acetylation followed by ring

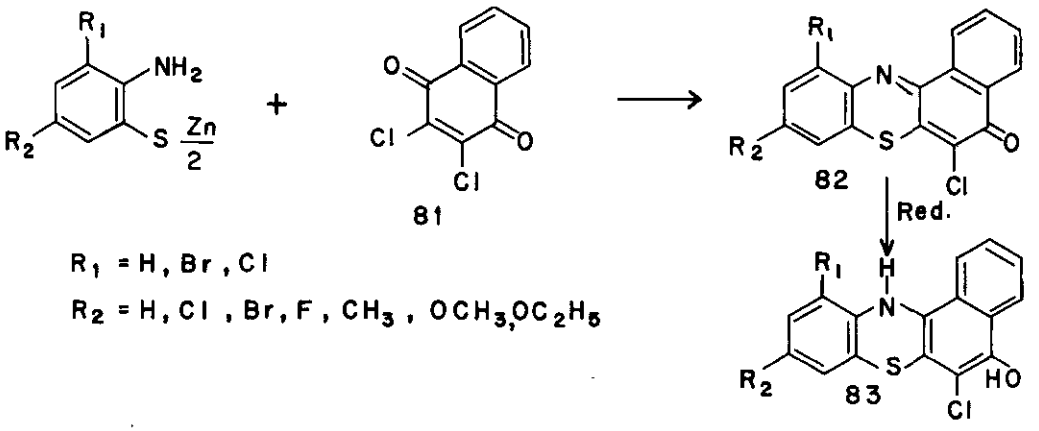


expansion via treatment with sulphuryl chloride gave the mixture of olefins 78 and 79.

Oxidation with DDQ in refluxing benzene followed by hydrolysis gave the observed product (80).

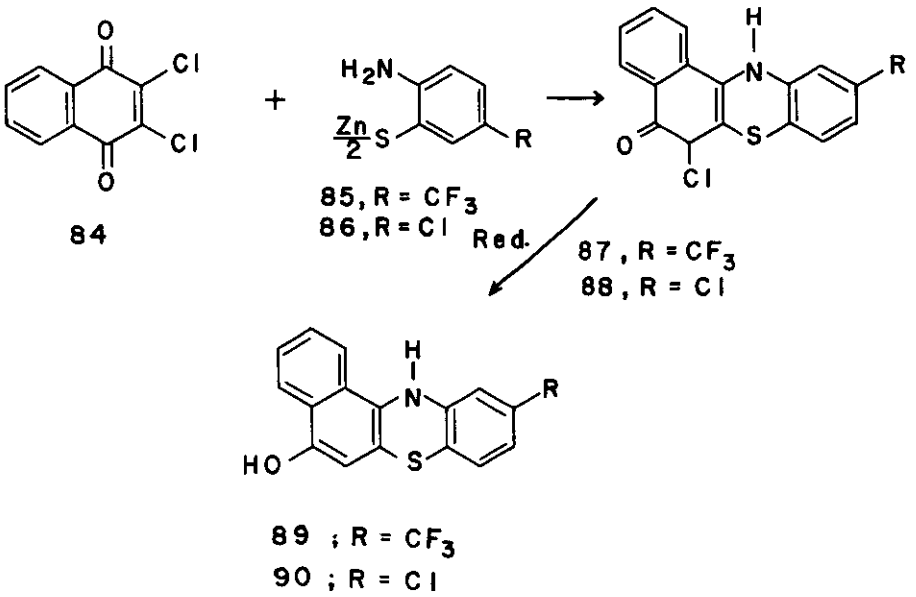
E. FROM QUINONES

A novel synthesis of 12-H-benzo(a)phenothiazine-5-ols has been reported by Agarwal and Mital[63]. They found that 2,3-dichloro-1,4-naphthoquinone (81) reacts with zinc mercaptides of substituted 2-aminothiophenols in alcohol to



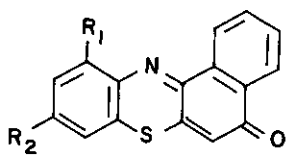
give the corresponding 5H-benzo[a]phenothiazin-5-one (82). Reduction with sodium hydrosulphite affords the corresponding 12H-benzo[a]phenothiazin-5-ols (83). The results are summarised in Table 6.

1,4-Naphthoquinone was also used in the synthesis of substituted phenothiazin-5-ones[65]. Thus condensation of 2,3-dichloro-1,4-naphthoquinone (84) with 4-trifluoromethyl or 4-chlorothiophenol zinc salt (85,86) resulted in the



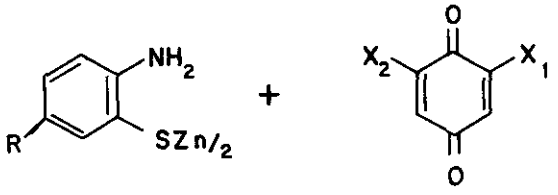
formation of 6-chloro-10-trifluoromethyl or 6,10-dichloro-5H-benzo[a]phenothiazin-5-one (87,88). Reduction of (87,88) gave benzo[a]phenothiazin-5-ol (89,90).

Table 6



R_1	R_2	% Yield	Ref.
H	H	90.5	63
H	Cl	90.6	
H	Br	92.8	
H	F	95.5	
H	CH_3	84.6	
H	OCH_3	85.4	
H	OC_2H_5	79.1	
Br	CH_3	80.4	
CH_3	CH_3	81.6	

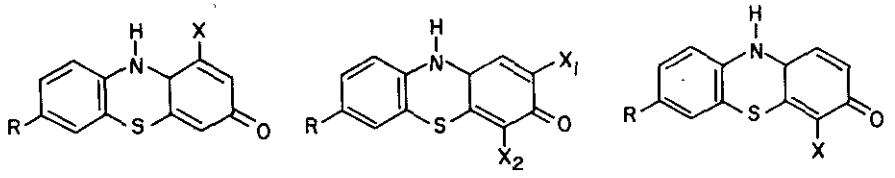
Syntheses of 1,7-disubstituted 3H-phenothiazin-3-ones (84-89) were achieved by reacting 5-substituted zinc 2-aminophenyl sulphides (90-92) with 2,6-di-substituted 1,4-benzoquinones (93-96). Two other products 2,4,7-trisubstituted phenothiazones (97-102) and 4,7-disubstituted 2-methyl-phenothiazones (103-104) were isolated as by-products[64]. Results are summarised in Table 7.



90, R = Cl
91, R = Br
92, R = CH_3

93, $X_1 = X_2 = Cl$
94, $X_1 = X_2 = Br$
95, $X_1 = Cl$, $X_2 = CH_3$

96, $X_1 = Br$, $X_2 = CH_3$



84, R = X = Cl
85, R = X = Br
86, R = Cl, X = CH_3
87, R = Br, X = CH_3
88, R = Br, X = CH_3
89, R = CH_3, X = Br

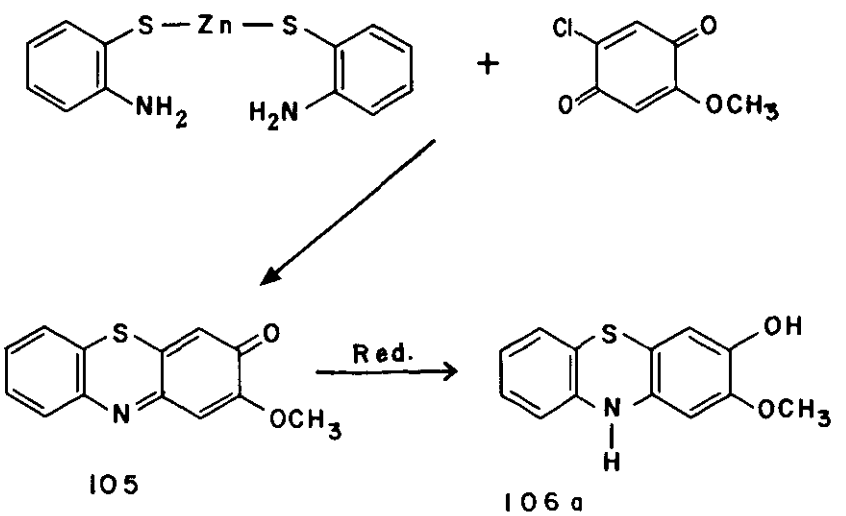
97, $R = X_1 = X_2 = Cl$
98, $R = X_1 = X_2 = Br$
99, $R = X_1 = Cl$, $X_2 = CH_3$
100, $R = X_1 = Br$, $X_2 = CH_3$
101, $R = CH_3$, $X_1 = X_2 = Cl$
102, $R = CH_3$, $X_1 = X_2 = Br$

103, R = X = Cl
104, R = X = Br

Table 7.

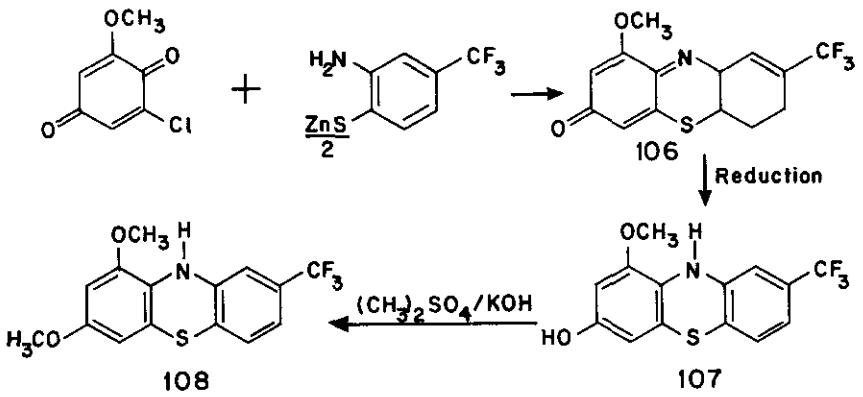
Starting Materials	3H-phenothiazin-3-one		% Yield
104 + 93	2,4,7-trichloro-	(97)	3.6
	1,7-dichloro-	(84)	52.6
91 + 94	2,4,7-trichloro-	(98)	1.6
	1,7-dibromo-	(85)	52.1
92 + 93	2,4-dichloro-7-methyl-	(101)	20.8
	1-chloro-7-methyl-	(88)	50.2
	2,4-dibromo-7-methyl-	(102)	10.4
92 + 94	1-bromo-7-methyl-	(89)	48.9
90 + 95	4,7-dichloro-2-methyl-	(103)	5.0
	2,7-dichloro-2-methyl-	(99)	7.6
	7-chloro-1-methyl-	(86)	38.7
	4,7-dibromo-2-methyl-	(104)	4.6
91 + 96	2,7-dibromo-4-methyl-	(100)	6.1
	7-bromo-1-methyl-	(84)	27.0

Another synthesis involving the condensation of 2-chloro-5-methoxy-1,4-benzoquinone with zinc salt of 2-aminothiophenol afforded 2-methoxyphenothiazin-3-one (105) in 88% yield. Reduction with sodium dithionite gave 2-methoxyphenothiazin-3-ol (106a)[65].

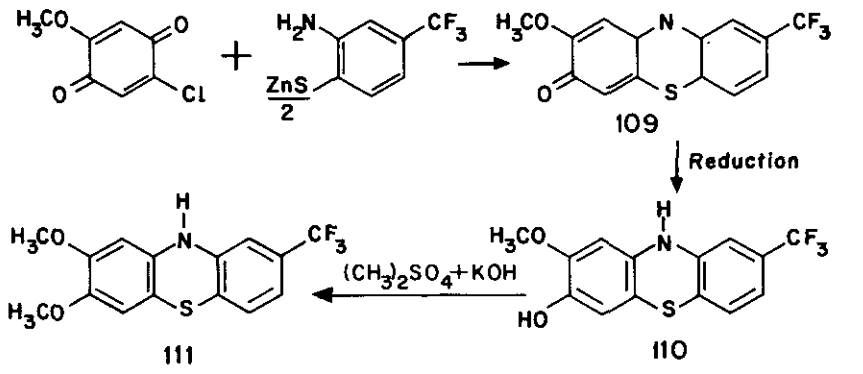


105 106a

Condensation of 2-chloro-6-methoxy-p-benzoquinone with 2-amino-4-trifluoromethylthiophenol zinc salt in ethanol at reflux for 4 h gave 2-trifluoromethyl-9-methoxyphenothiazin-7-one (106) in 70% yield[66]. Reduction with sodium hydrosulphite gave the corresponding alcohol (107) in 65% yield. Methylation with dimethyl sulphate/potassium hydroxide gave 2-trifluoromethyl-7,9-dimethoxyphenothiazine (108) in 70% yield.

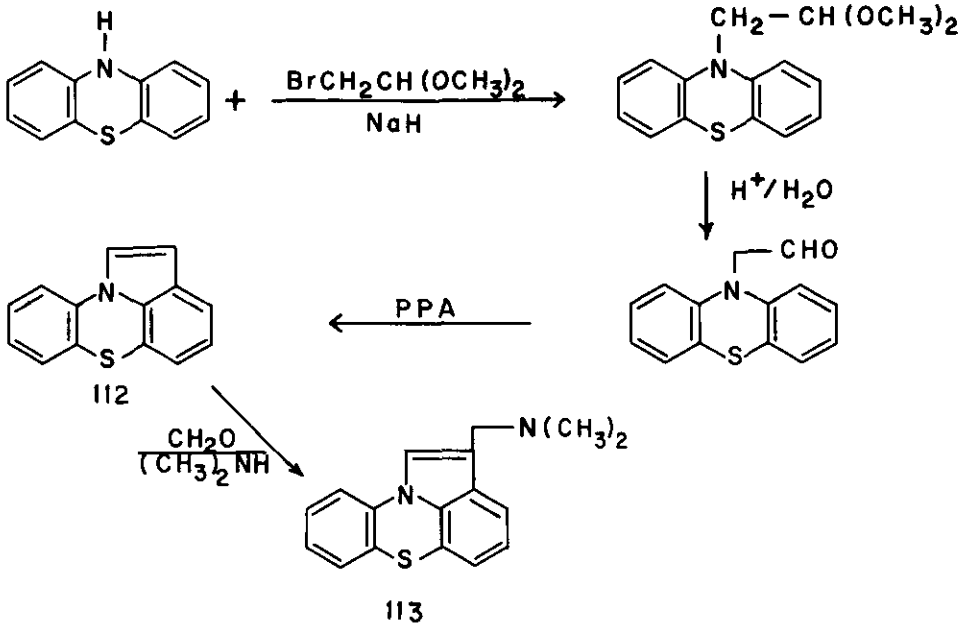


Similarly condensation of 2-chloro-5-methoxy-p-benzoquinone with zinc 2-amino-4-trifluoromethylthiophenol gave 8-methoxy-2-trifluoromethylphenothiazin-7-one, (109) which on reduction with sodium hydrosulphite gave the corresponding alcohol (110). Treatment with dimethyl sulphate/KOH gave 7,8-dimethoxy-2-trifluoromethylphenothiazine (111)[67,68].



F. SYNTHESIS OF FUSED PHENOTHIAZINES

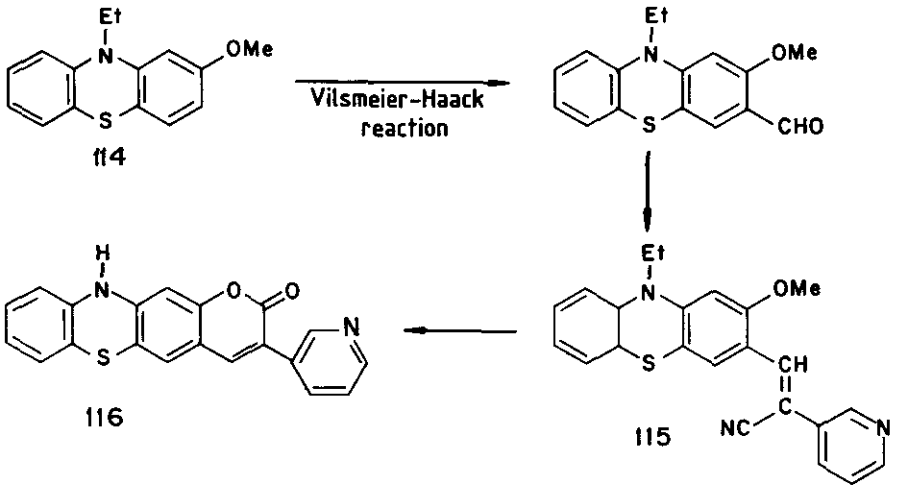
Pyrrolo[3,2,1-kl]phenothiazine (112), a compound having an interesting structure of combined phenothiazine and indole moieties, was obtained by alkylating phenothiazine with bromoacetaldehyde methyl acetal[69,70] and sodium hydride in



dioxan at reflux followed by hydrolysis to 113.

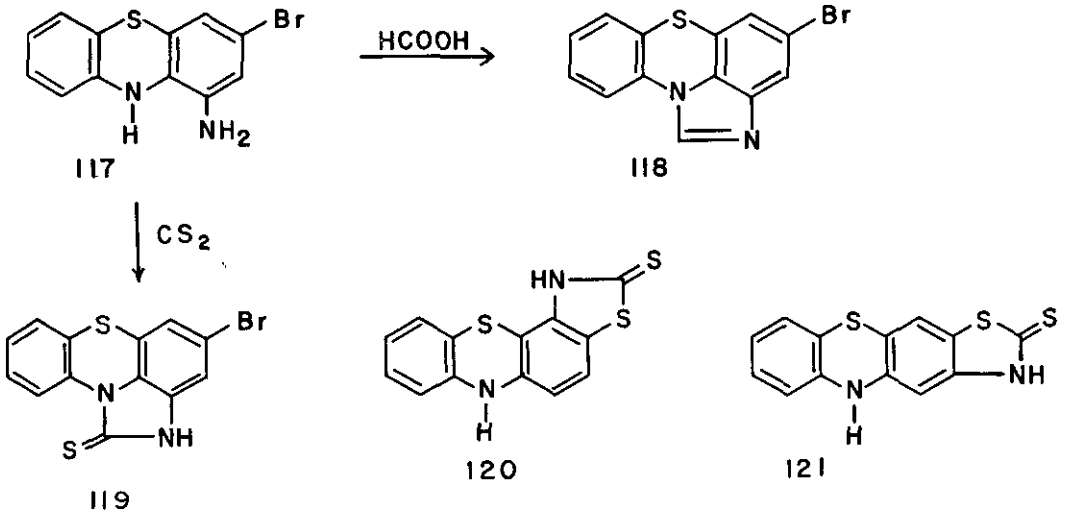
Cyclisation with polyphosphoric acid at room temperature afforded (112) in 84% yield. The Mannich condensation of (112) with formaldehyde and dimethylamine afforded 2-methylaminoethylpyrrolo[3,2,1-kl]phenothiazine (113)[70].

Phenothiazine derivative (116) was prepared by formylation of N-ethyl-2-methoxyphenothiazine (114) followed by condensation with heteryl-acetonitriles to yield the acrylonitrile (115), which was readily converted by pyridine hydrochloride



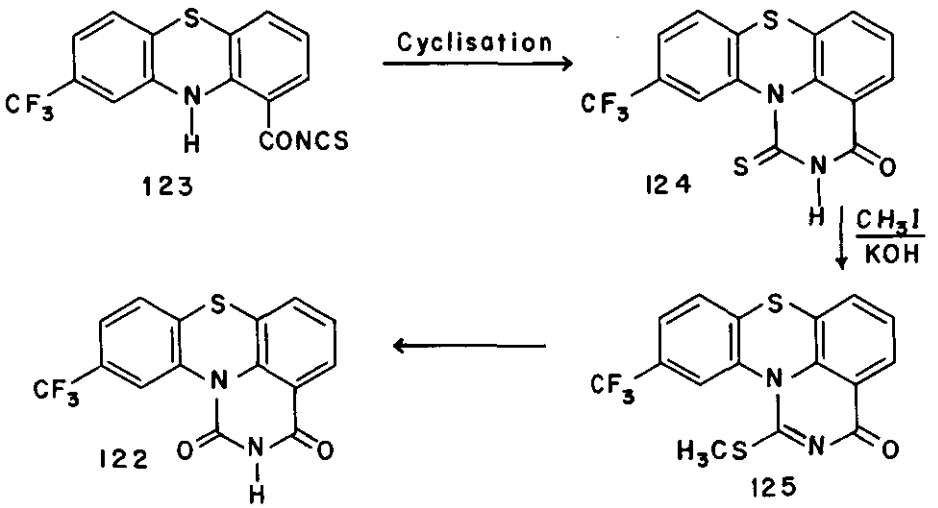
into 2-oxo derivative to the new heterocyclic system 2H-pyrano[6,5-b]phenothiazine (116)[71].

Refluxing 3-bromo-1-aminophenothiazine (117) and formic acid, pyrazolophenothiazine (118) was isolated in 80% yield. Treatment of (117) with carbon disulphide resulted in the formation of imidazolophenothiazine (119) in 44% yield. On the



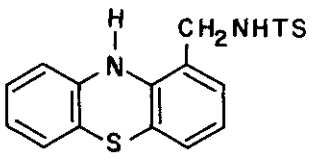
other hand 4-aminophenothiazine and carbon disulphide gave 25% of thiazolo-phenothiazine (120)[70]. Furthermore, phenylamino-2,3-dihydrobenzothiazole-2-thione reacted with sulphur and carbon disulphide at 170-180°C under pressure to yield 2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (121) in 50% yield[72].

10-Trifluoromethyl-2,3-dihydro-1H-pyrimido[5,6,1-kl]phenothiazine-1,3-dione (122) was synthesised by cyclising (123) in diphenyl ether at 220°C to yield (124) in 91% yield. Alkylation with iodomethane and potassium hydroxide in acetone gave (125) in 93% yield. Hydrolysis of (125) with hydrochloric acid in

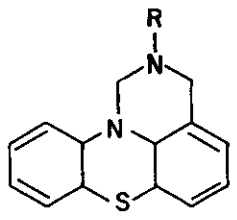


aqueous ethanol gave the target compound (122) in 98% yield[73].

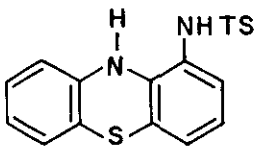
Synthesis of 1,3-dihydro-2H-pyrimido[5,6,1-kl]phenothiazine (126) was effected by reacting 1-tosylaminomethylphenothiazine (127) and methylene iodide. Similarly, 3-tosyl-1,2-dihydro-3H-pyrazino[3,2,1-kl]phenothiazine (128) and 1,2-dihydroimidazo[4,5,1-kl]phenothiazine (129) were prepared from (130) and



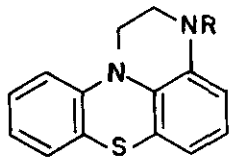
127



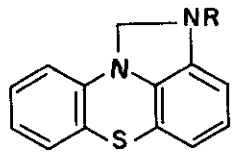
126, R = TS
131, R = H



130



128, R = TS
133, R = H



129, R = TS
132, R = H

ethylene dibromide or methylene iodide. Detosylation of the tosyl amides gave the corresponding fused phenothiazines (131, 132, 133)[74].

ACKNOWLEDGEMENT

The authors wish to thank Kuwait University for providing the financial support through Research Grant SC034.

REFERENCES

1. A. Bernthsen, Chem. Ber., 16, 2896 (1883).
2. S.P. Massie, Chem. Revs., 54, 797 (1954).
3. C. Bodea and I. Silberge, Advances in Heterocyclic Chem., 9, 321 (1968).
4. E.A. Nodiff and P.N. Craig, J. Org. Chem., 26, 824 (1961).
5. N.L. Smith, J. Org. Chem., 15, 1125 (1950).
6. A. Roe and W. Little, J. Org. Chem., 20, 1575 (1955).
7. E.A. Nodiff, S. Lipschutz, P.N. Craig, and M. Gordon, J. Org. Chem., 25, 60, (1960).

8. D. Chandra, V.N. Sharma, and R.L. Mital, Canad. J.Chem., 45, 761 (1967).
9. P.K. Kadaba and S.P. Massie, J. Org. Chem., 24, 986 (1959).
10. E.A. Nodiff and M. Hausman, J. Org. Chem., 29, 2453 (1964).
11. H. Brauniger and K.F. Ahrend, Pharmazie, 20, 758 (1965).
12. P. Jacquignon and J. Andre, C.R. Acad.Sc. Paris, 274, 1301 (1972).
13. M. Zander and W.H. Frank, Chem. Ber., 105, 3495 (1972).
14. Hung Teljis, Patent No.11, 419 (1967)., Chem. Abstr., 85, 78148d (1976).
15. V.V. Shavyrina, S.V. Zhuravler, Khim. Geterotriki. Soedin., 3, 243 (1971), Chem. Abstr., 78, 389 (1973).
16. N. Gospodenov, S. Levi, P. Filkov, and V. Genehev, Farmatsiya, 21 , 23 (1971).
17. J. Panasiewies, Z. Rybakow, M. Kaskiewiez, and J. Wiza, Radiochem. Radioanal. Letters., 33, 397 (1978).
18. Chem. Abstr., 85,3,2939,3 (1976).
19. Rom. Patent, 6,3 98,3 (1978) Chem. Abstr., 92, 22514x (1980)
20. J. Baryeki and B. Mastalerz, Chem. Stosow Ser. A., 12, 275 (1968).
21. Neth. Patent, 6, 605,036 (1966). Chem. Abstr., 66, 654924 (1967).
22. U.S. Patent, 3, 419,553 (1968). Chem. Abstr., 70, 7784b (1969).
23. J.I.G. Cadogan, R.K. Mackie, and M.J. Todd, Chem. Commun., 491 (1966).
24. S.V. Zhuravolv, A.N. Gribenko and Z.I. Erakova, Khim. Geterotsiki Soedin., 3, 235 (1971), Chem. Abstr., 78, 29692Y (1973).
25. S.V. Zhuravolv, A.N. Gribenko, and Z.I. Ermakova, Khim. Geterotsiki Soedin., 3, 240 (1971).
26. R.L. Mital and P.C. Tunk, Monatsh. 102, 760 (1971).
27. Fr. Demande, 2,207, 920 (1974).
28. J.I.G. Cadogan, S. Klik, C. Thomson and M.J. Todd, J. Chem. Soc., C, 2437 (1978).
29. J.K. Suzuki, A. Zirnis, and A.A. Manian, J. Heterocyclic Chem., 16, 1227 (1979).
30. J.I.G. Cadogan and R.K. Mackie, Org. Synth., 48, 113 (1968).
31. J.K. Suzuki and A. Zirnis, J. Heterocyclic Chem., 16, 1227 (1979).
32. D. Chandra, Ph.D. Thesis (1970), Rajashthan University, India.

33. Japan Patent, 7,337, 034 (1973), Chem. Abstr., 80, 1,209,47 (1974).

34. K.C. Ojah, S.K. Jain and R.R. Gupta, Syn. Commun., 9, 457 (1979).

35. R. Herz, Chem. Abstr., 23, 1140 (1929).

36. N.K. Goswami, S.K. Jain, and R.R. Gupta, Chem. Ind., 349 (1979).

37. K. Fuji, J. Pharm. Soc. Japan, 77, 3 (1957).

38. I. Oprean, C. Bodea, and V. Farcasan, Revue Chim., 15, 135 (1970).

39. V.A. Skorodumov, E.N. Llitschenko and S.V. Juravlev, Zhur. Obschehei Khim., 30, 1680 (1960).

40. C. Bodea, V. Farcasan and I. Oprean, Studii Si Cerceturi Chim. Acad. R.P.R. (Cluj), 14, 173 (1963).

41. G.P. Brown, J.W. Cole, and T.I. Cromwell, J. Org. Chem., 20, 1772 (1955).

42. N.K. Goswami, S.K. Jain, and R.R. Gupta, Ind. J. Chem., 18B, 274 (1979).

43. H.L. Sharma, V.N. Sharma, and R.L. Mital, Tetrahedron Letters, 17, 1657 (1967).

44. R.C. Chaudhary, Annales de la Societe Scientifique de Bruxelles., 93, 253 (1979).

45. R.R. Gupta, S.K. Jain, N.K. Goswami and G.S. Kalwania, Heterocycles, 14, 831 (1980).

46. R.L. Mital and S.K. Jain, J. Chem. Soc., C, 2148 (1969).

47. J. Teppema and L.B. Sebrel, Canad. Patent, 268, 922, Chem. Abstr., 21, 2273 (1927).

48. H.A. Lubs and J.R. Cole, U.S. Patent, 2, 025, 876, Chem. Abstr., 30, 1385 (1936).

49. K. Farrington and W.K. Warburton, Austr. J. Chem. 8, 545 (1955).

50. L.D. Huestis, M.L. Walsh, and N. Hahn, J. Org. Chem., 30, 2763 (1965).

51. F.F. Stephens and D.G. Wibberley, J. Chem. Soc., 3336 (1950).

52. Beltsteins Handbuch der Organischem Chemie, Vol. 13, Springer Verlag, Berlin, (1942), p. 591.

53. V.V. Sharyrina, S.V. Zhuravlev and I. Yu. Vikhkyaev, Khim. Pharm. Zh., 8, 23 (1974), Chem. Abstr., 81, 3659k (1974).

54. U.S. Patent, 3, 426, 020 (1967), Chem. Abstr., 70, 87832q (1969).

55. Japan Patent, 7, 528, 959 (1975), Chem. Abstr., 84, 1, 506, 45 , (1976).

56. V.N. Knyazev and V.N. Drozd, Zh. Org. Khim., 14, 893 (1978).

57. R.E. Chaudhary, An Auimca, 74, 173 (978).

58. M. Poulene and F. Daniel, Bull. Soc. Chim. France, 7, 2832 (1968).

59. L. Benati, P.C. Montevecchi and P. Spagnolo, Chem. Comm., 15, (1980).

60. R.R. Muceino, J. Cupano, and A.A. Liebmann, J. Heterocyclic Chem., 16, 605 (1979).

61. F. Chioccara, G. Prota, R.A. Nicolaus, and E. Novellino, Synthesis, 876 (1977).

62. F. Geiss, and G. Bleck, J. Labelled Compound., 4, 119 (1968).

63. N.L. Agarwal and R.L. Mital, Acta. Chimica Hungaricaa, 92, 89 (1977).

64. M.H. Terdic and L. Walter, Ann. Chem., 753, 1285 (1978).

65. N. Bhargava and R.L. Mital, Gazz. Ital. Chim., 109, 201 (1979).

66. A.R. Goyal and R.L. Mital, Nat and Appl. Sci. Bull, 29, 37 (1977).

67. A.R. Goyal, R.L. Mital, Gazz. Ital. Chim., 109, 205, (1979).

68. R.L. Mital, M. Mital, V. Lazami, S. Mital, and A.P. Shukla, J. int. Chem. (India), 50, 159 (1978).

69. R.A. Hollins and A.C. Pinto, J. Heterocyclic Chem., 15, 711 (1978).

70. R.D. Haugwitz and V.L. Narayanan, U.S. Patent, 3, 732, 215 (1973). Chem. Abstr., 77, 140106 (1972).

71. N.P. Buu Hoi, B. Lobert and S.R. Guermain, J. Chem. Soc., C, 2137 (1969).

72. V.V. Shavyrina and S.A. Zhravlev, Khim. Geterolsiki Soedin., 1, 38 (1972), Chem. Abstr., 77, 34407 (1972).

73. J. Weinstock, D.E. Gaitanopoulos, and B.M. Sutton, J. Org. Chem., 40, 1914 (1975).

74. H. Shira, H. Kayasaki and A. Toyahino, Chem. Pharm. Bull., 18, 1987 (1970).

Received, 8th April, 1986