THE CHEMISTRY OF PHENOTHIAZINE

SAMUEL P. MASSIE

Department of Chemistry, Fisk University, Nashville, Tennessee

Received July 1, 1954

CONTENTS

I. Introduction

Phenothiazine was first prepared by Bernthsen (12) in 1883 in the course of proof of structure studies on Lauth's violet and methylene blue. Since then it has played an important role in dye chemistry as the parent compound of the thiazine dyes (161). In the last twenty years phenothiazine and its derivatives have found numerous applications in other fields, and this has stimulated further research on these compounds.

Phenothiazine was discovered to have insecticidal properties in 1934 (26);

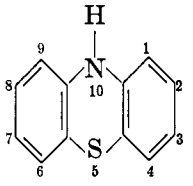
further work demonstrated its usefulness as an urinary antiseptic (43) and an antihelmintic (56). Its derivatives have been particularly valuable in human medicine as antihistamines (76, 78, 159), in the treatment of Parkinson's disease (24), and as antiemetics (61), to mention a few of their many applications. They have also been successfully employed as antioxidants (119).

Meyer and Jacobsen have given an excellent summary of the chemistry of phenothiazine up to 1920 with particular emphasis on its relation to methylene blue (112). Gilman's students (122, 142, 160) have reviewed the literature on phenothiazine in their doctoral dissertations. Metcalf (111) has discussed the chemistry of phenothiazine in his monograph on insecticides. Two excellent reviews on phenothiazine as an antihelmintic have appeared: a monograph by Beeler (8) and a chapter in a book by Findlay (56). Since no recent survey on phenothiazine chemistry has appeared, it seemed desirable to present a review on this subject, with special emphasis on the period from 1920 to 1953. This review deals only very briefly with the oxidized (quinonoid) forms of phenothiazine or the benzophenothiazines.

II. Nomenclature

Phenothiazine was first called thiodiphenylamine by Bernthsen (12), probably because of its synthesis from diphenylamine and sulfur. This practice still exists, but the preferred and more modern name is phenothiazine (127). It has also been called 2,3,5,6-dibenzo-1,4-thiazine (127) and dibenzoparathiazine (112).

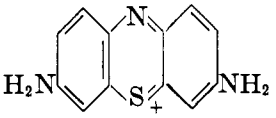
The numbering of the phenothiazine nucleus is as follows (127):



Derivatives prepared by substitution of the amino hydrogen are called 10-derivatives, and those involving the sulfur atom are called 5-derivatives. A brief discussion of the problems encountered in naming phenothiazine and its derivatives is given by Houston, Kester, and de Eds (87).

III. Historical

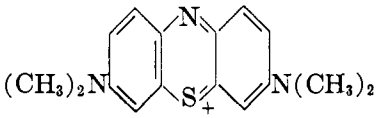
Perkin's synthesis of mauve and the founding of the synthetic dye industry stimulated many fields of organic research. Aromatic amines, in particular, were subjected to numerous types of reactions; phenothiazine chemistry had its beginning in such studies. Lauth (103) in 1876 heated *p*-phenylenediamine with sulfur and on treating the hydrochloric acid solution of the reaction product with ferric chloride obtained a purple dye. Caro (18) in the same year carried out a similar reaction with *p*-aminodimethylaniline and obtained a blue dye, later known as methylene blue.



Cl^-

Lauth's violet

3,7-Diaminophenothiazonium chloride



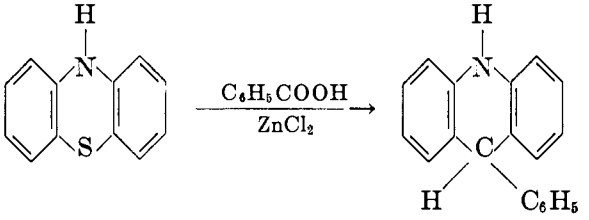
Cl^-

Methylene blue

3,7-Tetramethyldiaminophenothiazonium chloride

Bernthsen (12), the father of phenothiazine chemistry, in investigating the structure of the methylene blue dyes suspected the presence of the then unknown phenothiazine nucleus in these substances and prepared phenothiazine in 40 per cent yield by heating diphenylamine and sulfur at 250–260°C. He later (13) proved its structure in a series of interesting studies, some of which are described in the next paragraphs.

The presence of an amino group was shown by the preparation of methyl, ethyl, and acetyl derivatives (14). The presence of the sulfide linkage was demonstrated by the oxidation of 10-methylphenothiazine to the sulfone (15). The sulfide linkage was shown to be ortho to the amino group by converting phenothiazine to phenylacridine by the action of benzoic acid and zinc chloride (16).



Phenylacridine

Bernthsen nitrated phenothiazine with fuming nitric acid at 0°C., and obtained two dinitrophenothiazine sulfoxides, the so-called α- and β-isomers. The α-isomer was reduced to a diaminophenothiazine, which on oxidation gave thionine (Lauth's violet) (17). This series of reactions proved that the phenothiazine nucleus was present in thionine, and that in the α-isomer the nitro groups entered the para position. The structure of the β-isomer has not been proved.

Other workers continued to study the phenothiazine nucleus, some of the more interesting earlier work being that of Unger and Hoffman (157) on chlorination, of Kehrmann and his coworkers (91–98) on bromination and nitration, and of Smiles and his coworkers (52, 53, 164) on the preparation of phenothiazine derivatives by the rearrangement of *o*-aminodiphenyl sulfides. Interest in these compounds has been stimulated recently by the discovery of their physiological properties, particularly those of the 10-substituted derivatives (35, 78).

IV. Properties of Phenothiazine

Pure phenothiazine is a light yellow crystalline solid, melting at 180–181°C. (121). Smith and Nelson (144), nevertheless, found that material which had been sublimed at 130°C. at 1 mm. pressure had a melting point of 185.11°C. It is significant, however, that when the sublimed product was recrystallized, the highest melting point obtained was 184.21°C.

Phenothiazine is almost insoluble in water and is wetted only with difficulty. It is easily oxidized, particularly in the presence of sunlight and the slightest traces of moisture, and therefore is frequently obtained as a soft greyish or bluish-green powder. It has a faint but bitter taste. Phenothiazine is soluble in most of the common organic solvents, but only slightly soluble in ethanol.

Qualitatively, the presence of phenothiazine may be detected by the green color produced when an alcoholic solution of phenothiazine is treated with a very dilute ferric chloride solution, or by the deep red color obtained when an alcoholic solution of phenothiazine at 80°C. is treated with a slightly acidic solution of hydrogen peroxide (121). Phenothiazine itself may be used to detect the presence of certain metals (47).

Quantitatively, it may be determined gravimetrically (128, 152) by precipitation with chloroplatinic acid, following extraction with acetone, and colorimetrically by the red color (49) formed with bromine water or the blue color (37) obtained with palladous chloride.

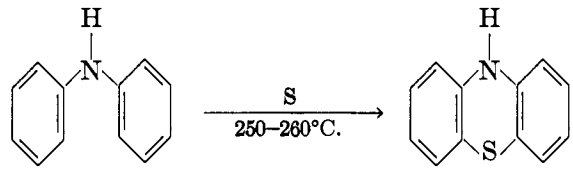
Its infrared spectrum has been recorded (145).

V. Preparation of Phenothiazine and its Derivatives

A. Ring-closure methods

1. Diphenylamine derivatives

As mentioned previously, the first preparation of phenothiazine involved the



Diphenylamine Phenothiazine

reaction of diphenylamine and sulfur at 250–260°C. (12). The conditions of reaction were greatly improved by the discovery (2, 101) that the addition of small amounts (1 per cent) of iodine as a catalyst lowered the temperature and time requirements and improved the yield. Aluminum chloride has also been found useful as a catalyst (1), and the use of a carbon dioxide atmosphere has been shown to improve the process by giving a purer product (62).

This reaction, referred to as thionation, has been widely used to prepare many substituted phenothiazines. Knoevenagel (101) used it in his early studies on substituted phenothiazines, as did Kehrmann and Dardel (92) in the prepara-

tion of some benzophenothiazines. 3-Methylphenothiazine (66) was prepared quantitatively by heating *p*-methyldiphenylamine, sulfur, and iodine at 280°C. for 20 min. Likewise, *p*-methoxydiphenylamine (4) and some long-chain alkyl ethers (88) yielded 3-alkoxyphenothiazines. *p*-Hydroxydiphenylamine on treatment with sulfur and iodine gave 3-hydroxyphenothiazine (87).

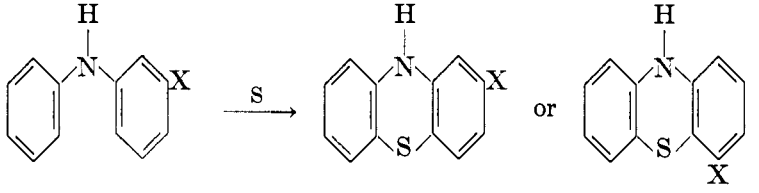
In a similar manner, *p*,*p*′-dihydroxydiphenylamine, sulfur, and iodine gave 3,7-dihydroxyphenothiazine (87). The fusion of sulfur, hydroquinone, and the appropriately para-substituted aniline gave 3-hydroxyphenothiazine (150), 3-hydroxy-8-methylphenothiazine, and 7-ethoxy-3-hydroxyphenothiazine (151).

Fluorodiphenylamines have been shown to undergo thionation (133, 145) to give fluorophenothiazines. *p*-Anilinophenoxyacetic acid formed 3-phenothiazineacetic acid (4), but the corresponding methyl ester did not undergo cyclization. Likewise, neither *o*-carboxydiphenylamine nor its ethyl ester would undergo cyclization (68).

Sulfuryl chloride has also been used as a thionating agent (86). The reaction of diphenylamine and sulfuryl chloride gave a 15 per cent yield of phenothiazine.

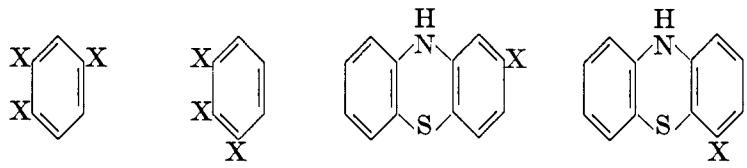
The ability of *N*-substituted diphenylamines to undergo thionation has not been fully established. Some workers have been unable to form phenothiazine derivatives from *N*-substituted diphenylamines (13, 109), but Desai (45) found that 10-benzylphenothiazine could be prepared from *N*-benzyldiphenylamine and sulfur. This compound was also obtained from 10-sodiophenothiazine and benzyl chloride (66), and by the reaction of 2-benzyloxyquinoline and phenothiazine (69).

Smith (145), in the studies of fluorophenothiazine reported above, was concerned with the orientation of meta-substituted diphenylamines on thionation. While ortho-substituted diphenylamines obviously would give 1-substituted phenothiazines, and para-substituted diphenylamines would give 3-substituted phenothiazines, meta-substituted diphenylamines could give 2- or 4-derivatives.



Previous orientation studies on the position of entering groups in the formation of phenothiazine derivatives (4, 66, 67) had shown that there were no rules for predicting their position, and that chemical methods of identification offered little promise of distinguishing between the 2- and the 4-isomer.

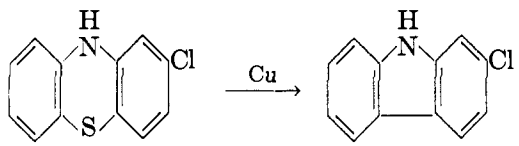
Smith, therefore, resorted to infrared spectral analysis for proof of orientation. As a guide he used the work of Barnes, Gore, Stafford, and Williams (5), who showed that asymmetrically substituted benzenes (A) have characteristic frequencies in the 12.0–12.5 μ region, while vicinally trisubstituted benzene compounds (B) absorb in the 12.5–13.15 μ region. In accordance with these



A B C D

facts, the 2-substituted phenothiazines (C) should absorb in the 12.0–12.5 μ region, while the 4-derivatives (D) should have bands in the region from 12.5 to 13.15 μ. In the spectrum of the product obtained by the thionation of *m*-trifluorodiphenylamine, there was a band at 12.17 μ which was not found in the spectrum of unsubstituted phenothiazine, and Smith therefore postulated that the 2-isomer was formed.

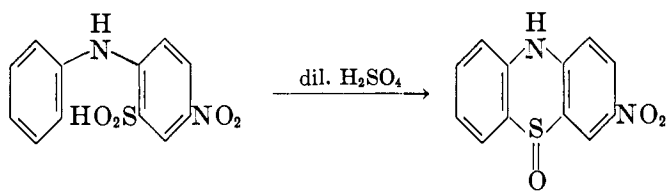
The thionation of *m*-methyldiphenylamine and *m*-chlorodiphenylamine gave both the 2- and the 4-isomer, although the 2-isomer was formed in greater yield (33). The positions were proved by conversion to the corresponding



carbazoles through heating with copper (72). On the other hand, *m*-methoxydiphenylamine gave only the 2-isomer.

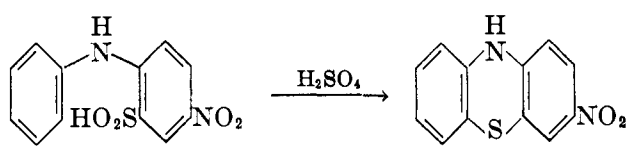
2. Diphenylaminosulfinic acids

Krishna and Jain (102) found that when the blue solution obtained by dissolving 4-nitrodiphenylamine-2-sulfinic acid in sulfuric acid was immediately diluted with water, 3-nitrophenothiazine 5-oxide was obtained.



3-Nitrophenothiazine 5-oxide

If, however, the solution was allowed to stand for 30 min. before dilution, sulfur dioxide was evolved and 3-nitrophenothiazine was formed.

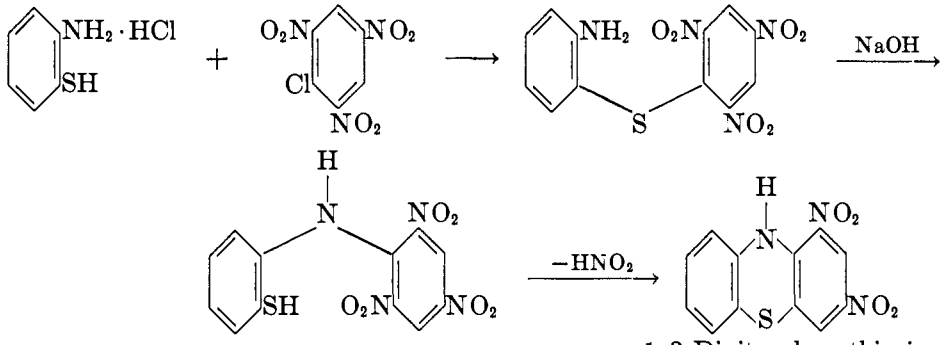


3-Nitrophenothiazine

Evans and Smiles (52) found that on adding hydriodic acid to a warm aqueous solution of 4-nitrodiphenylamine-2-sulfinic acid, 3-nitrophenothiazine was formed. Smiles and Warren (162) showed that in hot acetic acid *N*,4-dimethyl-2-nitrodiphenylamine-2-sulfinic acid underwent cyclization with the liberation of the oxides of nitrogen to give 3,10-dimethylphenothiazine.

3. Smiles rearrangement

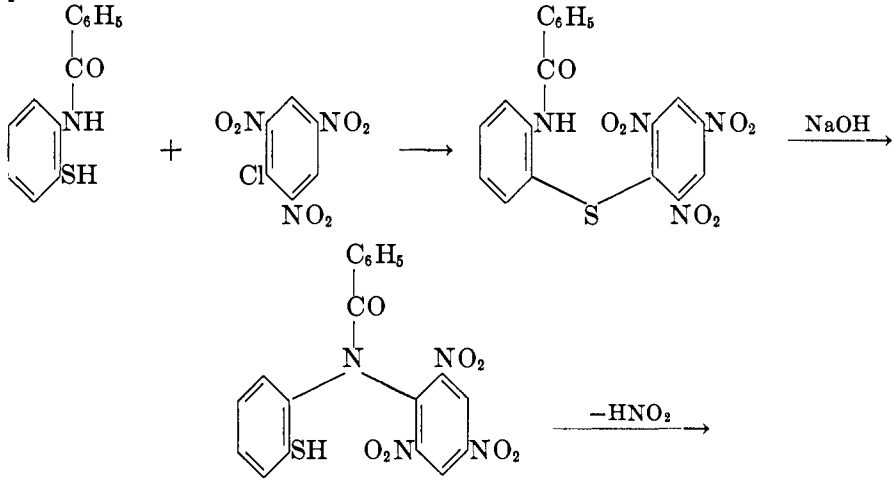
The reaction of picryl chloride and *o*-aminothiophenol hydrochloride, followed by treatment with alkali, gave 1,3-dinitrophenothiazine (97). The same com-

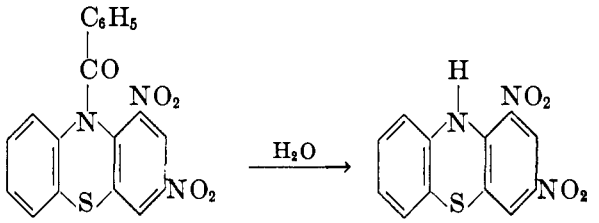


1,3-Dinitrophenothiazine

pound was obtained by the reduction of bis-2-picramidodiphenyl disulfide, followed by treatment with alkali (96).

Other workers (117, 118) sought to prepare the isomeric 2,4-dinitrophenothiazine. They converted 2-benzamidothiophenol into 2-benzamidophenyl picryl sulfide by reaction with picryl chloride in the presence of sodium acetate. This sulfide on treatment with alkali gave an *N*-benzoyldinitrophenothiazine, which on hydrolysis yielded a product melting 30 degrees higher than the previously reported 1,3-dinitrophenothiazine. However, it was shown (95) that the two products were the same, and that the reaction gave 1,3-dinitrophenothiazine.

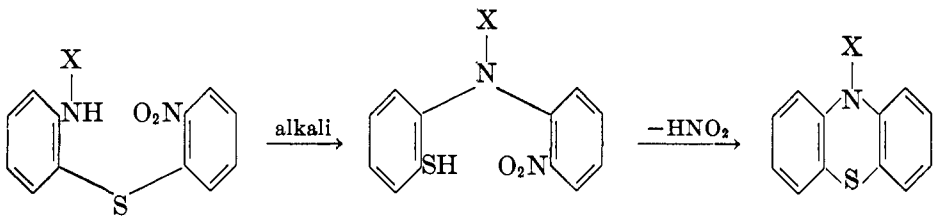




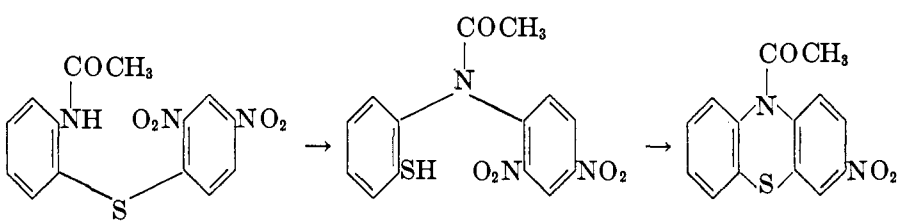
1,3-Dinitrophenothiazine

It was suggested that the higher melting product may have been another crystalline form of 1,3-dinitrophenothiazine or incompletely converted sulfide (95).

These results could not be correlated until Smiles and his coworkers (52, 53, 164) showed that rearrangements of 2-nitro-2′-acylaminodiphenyl sulfides to 2′-mercapto-2-nitro-*N*′-acyldiphenylamines took place readily in alkaline media and that these compounds, in turn, lost nitrous acid to form phenothiazines.

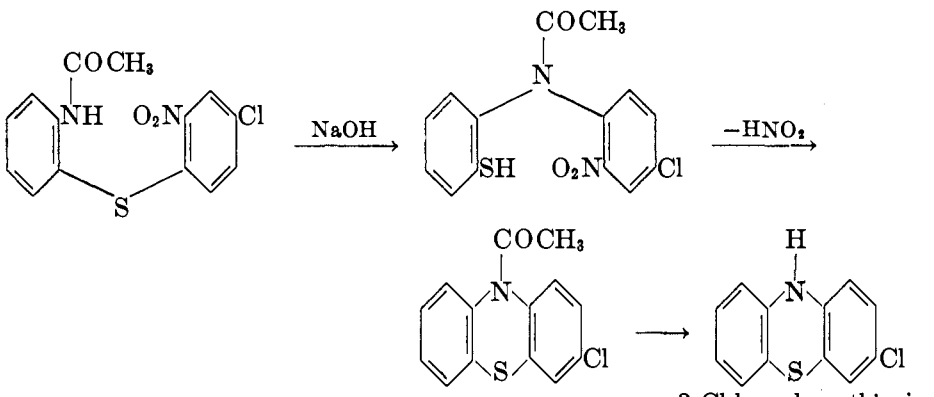


This rearrangement was found to be one of a class of rearrangements, called the Smiles rearrangement (9). It has been found to be useful in the preparation of some phenothiazine derivatives, although it fails in others. 2′-Acetamido-2,4-dinitrodiphenyl sulfide readily underwent rearrangement in an acetone–alcohol solution containing sodium hydroxide to give *N*-acetyl-2′-mercapto-2,4-dinitrodiphenylamine, which on boiling gave 10-acetyl-3-nitrophenothiazine (164).



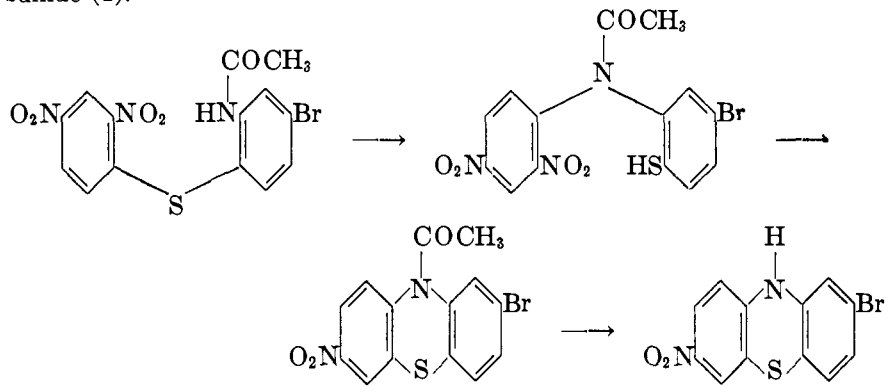
10-Acetyl-3-nitrophenothiazine

Likewise, 2′-acetamido-4-chloro-2-nitrodiphenyl sulfide underwent rearrangement to give, subsequent to hydrolysis, 3-chlorophenothiazine (164).



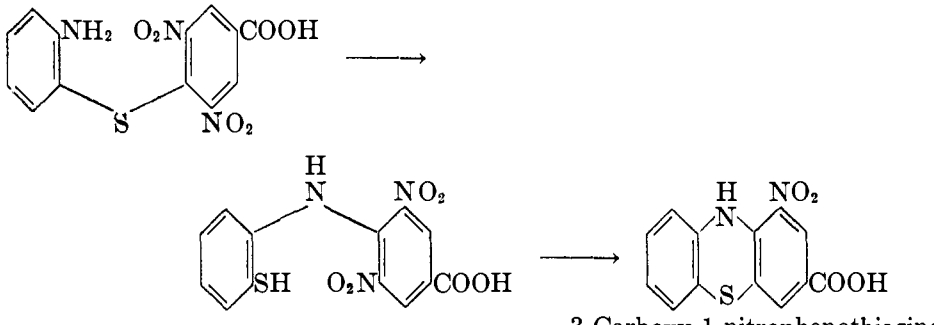
3-Chlorophenothiazine

2-Bromo-7-nitrophenothiazine was prepared in 64 per cent yield by the rearrangement and cyclization of 2-acetamido-4-bromo-2′,4′-dinitrodiphenyl sulfide (4).



2-Bromo-7-nitrophenothiazine

These same workers (4) found, however, that neither 2-acetamido-4-bromo-2′-nitrodiphenyl sulfide nor 2′-acetamido-4-carboxy-2-nitrodiphenyl sulfide would undergo cyclization. This last failure is in contrast to the successful rearrangement and cyclization of 2′-amino-4-carboxy-2,6-dinitrodiphenyl sulfide to form 3-carboxy-1-nitrophenothiazine (156).



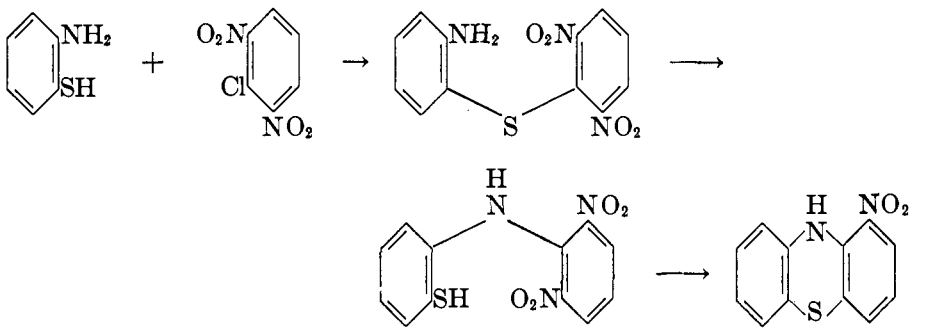
3-Carboxy-1-nitrophenothiazine

It will also be noted that the last-mentioned rearrangement involved not the acylated amine, as Evans and Smiles (52) stated was necessary, but the free amine. Other examples involving the use of the free amine include the preparation of 8-chloro-1,3-dinitrophenothiazine from the reaction between 2-amino-4-chlorothiophenol and picryl chloride on the immediate addition of a concentrated aqueous solution of sodium acetate (130).

When a solution of *o*-aminothiophenol hydrochloride in boiling water was treated with 4-chloro-3,5-dinitrobenzenesulfonic acid and sodium acetate, followed by treatment with potassium hydroxide, 1-nitrophenothiazine-3-sulfonic acid was obtained as the potassium salt (56).

In the same manner, 2-chloro-3,5-dinitrobenzenesulfonic acid gave potassium 3-nitrophenothiazine-1-sulfonate (156).

The reaction of *o*-aminothiophenol, 2,6-dinitrochlorobenzene, and sodium acetate in refluxing alcohol for 24 hr. gave a poor yield of 1-nitrophenothiazine (94).



1-Nitrophenothiazine

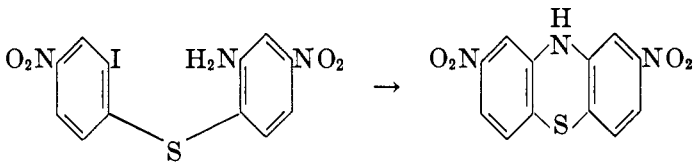
These varied results demonstrate that the Smiles rearrangement is affected by many factors. For example, when the halogen (chlorine) was in the same ring as the nitro group in a halomononitroacetamidodiphenyl sulfide, rearrangement and cyclization took place (164). When the halogen (bromine) was situated in a different ring from the nitro group, however, no cyclization occurred (4). But even though the halogen (bromine) was in a different ring, the presence of two nitro groups in the same ring caused rearrangement and ring-closure (4). Finally, although a carboxyl in the same ring as the nitro group did not cause cyclization (4), in the presence of two nitro groups the carboxyl derivative did undergo cyclization (156). It thus appears that rearrangement and ring-closure depend on many factors; further study of these factors might increase the utility of this rearrangement as a route to phenothiazine derivatives.

4. Diphenyl sulfides

In contrast to the ready formation of phenothiazine derivatives by the ring-closure of diphenylamine derivatives, only a few cases of ring-closure involving diphenyl sulfide derivatives have been reported.

As was shown in the history of the Smiles rearrangement, earlier workers (96, 97, 117, 118) thought that they had prepared phenothiazine derivatives by the ring-closure of diphenyl sulfides and sulfones, but it was shown (52) that rearrangement of the sulfides or sulfones to diphenylamine thiols or sulfinic acids preceded the ring-closure.

The first definite formation of a phenothiazine derivative by ring-closure of a diphenyl sulfide was reported by Michels and Amstutz (115), who prepared 2,8-dinitrophenothiazine in 50 per cent yield by the heating, at 220–230°C. for 30 hr., of a mixture of 2-amino-2′-iodo-4,4′-dinitrodiphenyl sulfide, cuprous iodide, and sodium carbonate.



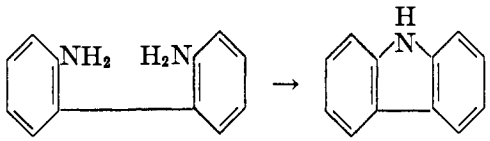
2,8-Dinitrophenothiazine

These workers ruled out the possibility of a Smiles rearrangement on the grounds that if rearrangement did occur the only possible product would be 2,7-dinitrophenothiazine. The identity of the diaminophenothiazine dioxide from this ring-closure with that obtained from the Friedel–Crafts reaction of *N*-acetylphenothiazine and acetyl chloride would thus have meant that the acetyl groups entering in the Friedel–Crafts reaction assumed positions meta to the nitrogen in one case and para to the nitrogen in the other case. Such unsymmetrical substitution seemed unlikely.

Hodgson, Dodgson, and Smith (84) were unable to prepare any phenothiazine derivatives by the ring-closure of diphenyl sulfides. The reduction of 2,2′,4,4′-tetranitrodiphenyl sulfide was attempted in the hope that the tetraamine might undergo cyclization to form 2,8-diaminophenothiazine during the process of reduction, but only *m*-phenylenediamine was obtained. These workers also were unable to cyclize either 2′-amino-2-chloro-4,4′-dinitrodiphenyl sulfide by heating it in nitrobenzene with potassium carbonate and cuprous chloride at 180°C. for 7 hr., or 2,2′-diamino-4,4′-dinitrodiphenyl sulfide.

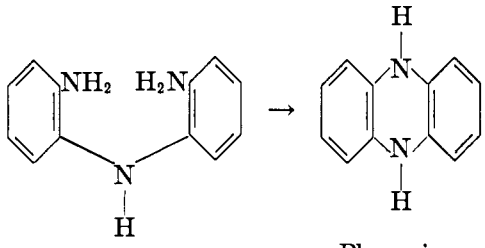
In a similar manner the attempted cyclization of 2,2′-diamino-4,4′-diiododiphenyl sulfide (115) was unsuccessful, as were attempts to form ring compounds by the reaction of 2,2′-diaminodiphenyl sulfide with 2-bromo-3-nitrobenzoic acid or potassium *o*-chlorobenzoate (67).

A similar difficulty of ring-closure of diphenyl ether derivatives has been noted (110). 2,2′,4,4′-Tetraaminodiphenyl ether could not be cyclized by heating the hydrochloride alone or with zinc chloride in an atmosphere of carbon dioxide for 20 hr. at 200°C. In the preparation of the tetraamine, by the reduction of the tetranitro compound with stannous chloride, an appreciable amount of oxygen was liberated, corresponding to the analogous elimination of sulfur for the sulfide analog. The failure of these diphenyl ethers and diphenyl sulfides to undergo cyclization is in sharp contrast to the ease with which 2,2′-



Carbazole

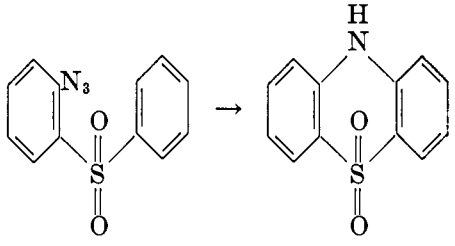
diaminobiphenyl (153) and 2,2′-diaminodiphenylamine (47) undergo cyclization to carbazole and phenazine, respectively.



Phenazine

Hodgson (84) explained this difficulty on the basis of the non-coplanarity of the benzene rings in the sulfide and ether, and supported this view with an example of the difference in the affinity of cotton for dyes made from 4,4′-diaminodiphenylamine and from 4,4′-diaminodiphenyl sulfide (85). He also pointed out that in a diphenylamine the whole molecule can resonate and is therefore coplanar, whereas in an *o*,*o*-diaminodiphenyl sulfide resonance is prevented, so that in a diphenylamine cyclization with sulfur will be facilitated, whereas elimination of ammonia from *o*,*o*-diaminodiphenyl sulfide would be hindered.

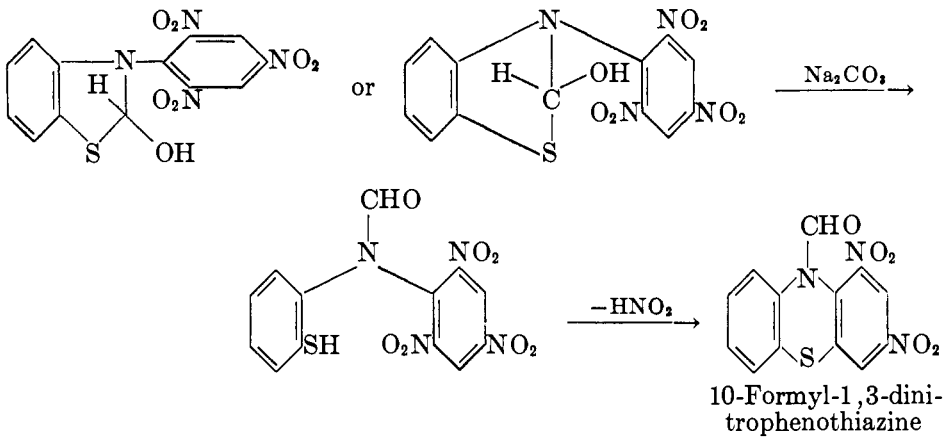
A ring-closure of recent discovery is the cyclization of *o*-azidodiphenyl sulfone by heating the sulfone in decalin with the evolution of nitrogen and the formation in 16 per cent yield of phenothiazine 5-dioxide (147).



Phenothiazine 5-dioxide

5. Miscellaneous ring-closure methods

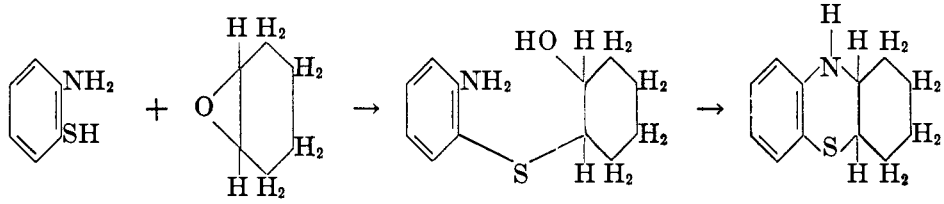
The action of hot aqueous sodium carbonate on 2-hydroxy-3-picryl-2,3-dihydrobenzothiazole gave a quantitative yield of 10-formyl-1,3-dinitrophenothiazine (155).



10-Formyl-1,3-dinitrophenothiazine

The action of oleum on diphenylamine at 50–80°C. yielded tetrasulfonic acid derivatives of phenothiazine 5-dioxide (54, 55). The sulfonic acid groups could be removed by hydrolysis with dilute mineral acids, and thus the use of variously substituted diphenylamines with unsubstituted ortho nitrogen positions gave derivatives of phenothiazine 5-dioxide.

A refluxing solution of cyclohexene oxide and *o*-aminothiophenol in alcoholic potassium hydroxide gave 1,2,3,4,*x*,*x*-hexahydrophenothiazine in 99 per cent yield (36). This is one of the few examples of a reduced ring in phenothiazine



chemistry. *o*-Aminothiophenol and 1,2-dihydroxy-4-*tert*-octylbenzene[1] gave 4-*tert*-octylphenothiazine (123).

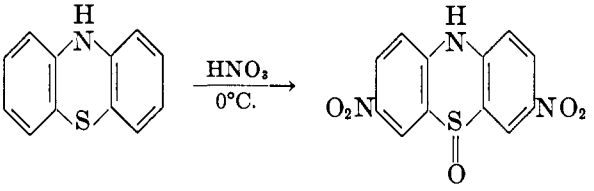
B. NUCLEAR SUBSTITUTION REACTIONS

Substituents have been introduced directly into the phenothiazine nucleus by five principal methods: (*1*) nitration, (*2*) halogenation, (*3*) mercuration, (*4*) metalation, and (*5*) acylation *via* the Friedel–Crafts method. Of these five, nitration and halogenation also give rise to oxidation and complex products. Conspicuously absent in the literature is the direct sulfonation of phenothiazine. The action of sulfuric acid on phenothiazine to give 7-hydroxyphenothiazone-3 is, however, mentioned (73, 87). Other groups have, in turn, replaced these directly introduced substituents.

[1] *tert*-Octyl = $(CH_3)_3CCH_2\overset{|}{C}(CH_3)_2$.

1. Nitration

As previously cited, Bernthsen (17) nitrated phenothiazine with fuming nitric acid at 0°C. and obtained two dinitrophenothiazine sulfoxides, the so-called α- and β-isomers. The α-isomer was shown to be 3,7-dinitrophenothiazine 5-oxide, whereas the structure of the β-isomer has never been proved.



3,7-Dinitrophenothiazine 5-oxide

By using more moderate conditions of nitration, Bernthsen (17) obtained a mononitrosulfoxide. Reduction of this nitro derivative gave an amine, which on oxidation with ferric chloride formed a dye of the methylene blue family. Since it had been shown that this behavior was characteristic of 3-aminophenothiazines, the mononitro compound was identified as 3-nitrophenothiazine 5-oxide.

The nitration of 10-methylphenothiazine gave 10-methyl-3-nitrophenothiazine 5-oxide and 10-methyl-3,7-dinitrophenothiazine 5-oxide (99). The structures of these compounds were proved by comparing them with products obtained by the methylation of 3-nitrophenothiazine 5-oxide and 3,7-dinitrophenothiazine 5-oxide.

Phenothiazine on heating in an open vessel with fuming nitric acid was reported to yield a tetranitrophenothiazine 5-oxide (6, 94). Barnett and Smiles (6) reduced this nitro compound to diaminothionine, but other workers (94) could not duplicate this work. The latter workers also obtained a trinitrophenothiazine 5-oxide.

The nitration of 10-acetylphenothiazine with nitric acid in acetic acid gave 3,7-dinitrophenothiazine 5-oxide (17, 66). Gilman and Shirley (66) also obtained the 3-nitrophenothiazine 5-oxides by the nitration of 10-ethyl-, 10-decyl-, 10-octadecyl-, and 10-phenylphenothiazines.

When powdered sodium nitrite was added to a suspension of phenothiazine in glacial acetic acid, the chief product was 3,7-dinitrophenothiazine (94). The addition of 4 moles of powdered sodium nitrite to a suspension of 1,3-dinitrophenothiazine in cold glacial acetic acid yielded 1,3,7-trinitrophenothiazine (95).

2. Halogenation

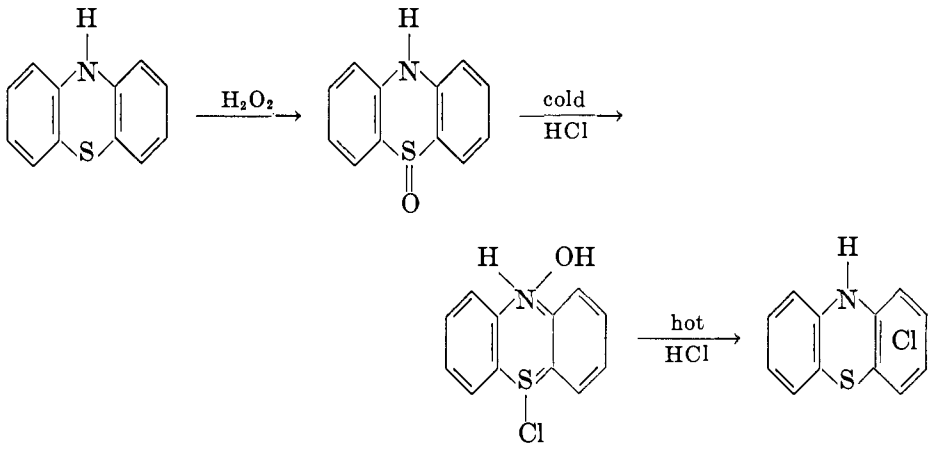
Fluorine has not been directly introduced into the phenothiazine nucleus. The fluorophenothiazines have been prepared by the thionation of some fluorodiphenylamines (133, 145).

The direct chlorination of phenothiazine is reported to give very small yields of di- and tetrachlorophenothiazines, and some tetrachlorophenothiazine 5-dioxide (157). Since the dichloro derivative upon nitration, reduction, and treat-

ment with ferric chloride did not give a dye, it was assumed that nitration did not occur at the 3-position, probably because the 3-position was already occupied, and the chlorine derivative was assumed to be 3,7-dichlorophenothiazine.

These same authors found that treatment of an ethereal hydrogen chloride solution of phenothiazine with nitrogen tetroxide also caused chlorination, and they obtained mono-, di-, and tetrachlorophenothiazines. The tetrachloro derivative was found to be identical with the product obtained by direct chlorination. The dichloro derivative was found to be isomeric with the direct chlorination product, and from nitration studies was assumed to be 1,3-dichlorophenothiazine. The monochloro derivative could not be purified.

This latter method of chlorinating phenothiazine was further investigated by Page and Smiles (126), who showed that this reaction takes place through rearrangement of the phenothiazonium salt. The postulated mechanism was as follows:



The reaction proceeds only slightly with hydrobromic acid (50, 126), and not at all with hydriodic acid and appears, therefore, to depend upon the halogen acid. It also depends upon the nature and number of substituents in the phenothiazine nucleus, for 3,7-dinitrophenothiazine was unattacked by the reagent (126), whereas 10-methylphenothiazine gave only one product, 3-chloro-10-methylphenothiazine (126), and 10-ethylphenothiazine 5-oxide with hydrochloric acid gave a 68 per cent yield of 3-chloro-10-ethylphenothiazine (63). Kehrmann and Nossenko (94) found that treatment of 3-nitrophenothiazine 5-oxide in glacial acetic acid with hydrogen chloride gave 7-chloro-3-nitrophenothiazine.

Treatment of phenothiazine with bromine gave 3,7-dibromophenothiazonium bromide (98), or the hydrobromide of phenothiazonium bromide (93, 131).

The action of iodine on phenothiazine gave the hydroiodide of phenothiazonium iodide (131). Iodine will also replace a metal to give iodophenothiazines. 10-Ethyl-4-lithiophenothiazine and iodine gave 10-ethyl-4-iodophenothiazine (63).

3. Mercuration

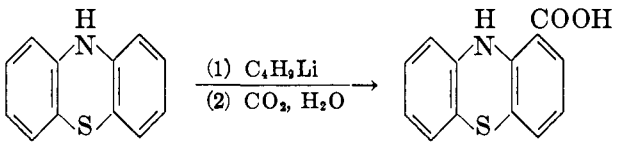
10-Methyl- and 10-ethylphenothiazines were shown to react with ease with an alcoholic solution of mercuric acetate to yield a mixture of 3-acetoxymercuri- and 3,7-diacetoxymercuri-10-alkylphenothiazines (57, 63, 160).

These two substances could easily be separated, since the monoderivative is soluble in hot ethanol. The acetoxymercuri groups were converted to chloromercuri groups by treatment with sodium chloride, and these chloromercuri derivatives, upon treatment with potassium iodide, bromine in potassium bromide solution, or arsenic trichloride, yielded the corresponding iodide, bromide, or arsenious chloride.

The structures of the mercury derivatives of 10-methylphenothiazine were proven by replacement of the acetoxymercuri groups with nitro groups. Upon treatment with concentrated nitric acid they yielded a dinitrosulfoxide identical with Kehrmann and Zybs's (99) 10-methyl-3,7-dinitrophenothiazine 5-oxide, and 10-methyl-3-nitrophenothiazine 5-oxide.

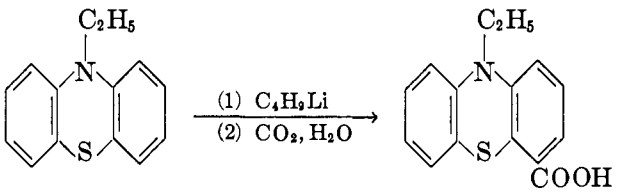
4. Metalation

Phenothiazine has been shown to be metalated by butyllithium in the 1-position to give, on carbonation, a 52 per cent yield of phenothiazine-1-carboxylic acid (67).



Phenothiazine-1-carboxylic acid

In contrast, 10-ethyl- and 10-phenylphenothiazines were metalated by butyllithium in the 4-position, but in poor yield (68).



10-Ethylphenothiazine-4-carboxylic acid

The metalation of 3-methoxyphenothiazine with butyllithium gave, on subsequent carbonation, a monocarboxylic acid; the position of the carboxyl group was not determined (4) but was assumed to be 1 or 4.

The lithium atom may also be replaced by halogens. 10-Ethyl-4-lithiophenothiazine, upon treatment with iodine, gave 10-ethyl-4-iodophenothiazine (63).

Nelson metalated phenothiazine and some 10-substituted phenothiazines and treated the lithium derivative with benzophenone to obtain the corresponding

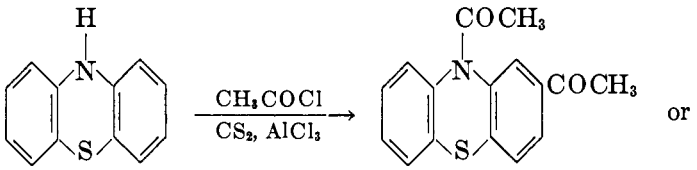
phenothiazyldiphenylcarbinols (122). In the case of 10-[2-(1-pyrrolidylethyl)]-phenothiazine, a dicarbinol was obtained, showing dimetalation, but phenothiazine itself and 10-ethylphenothiazine gave only monocarbinols.

Nelson likewise obtained 10-ethylphenothiazine-4-carboxylic acid from the metalation of 10-ethylphenothiazine 5-oxide by butyllithium, thus showing that reduction of the sulfoxide and metalation of the nucleus took place simultaneously.

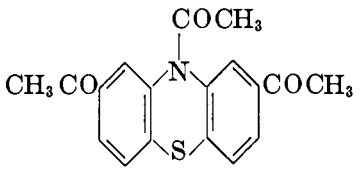
5. Acylation via the Friedel–Crafts reaction

The first Friedel–Crafts reaction involving phenothiazine was carried out by Scholl and Seer (137), who reacted phenothiazine, phthalic anhydride, and aluminum chloride in refluxing carbon disulfide and obtained, in poor yield, a compound which they called phenothiazine-3,7-diphthaloylic acid. This compound on cyclization yielded a bisquinone which they regarded as linear. Later workers repeated this work and also reported a poor yield (4). Under similar conditions 10-methylphenothiazine gave a 25 per cent yield of a diphthaloylic acid, which, in turn, gave a linear bisquinone also considered to be a 3,7-derivative.

The reaction of 10-acetylphenothiazine with acetyl chloride and aluminum chloride in refluxing carbon disulfide has been shown to give 2,10-diacetylphenothiazine (4) and 2,8,10-triacetylphenothiazine (115), depending on the amount of acetyl chloride used.



2,10-Diacetylphenothiazine



2,8,10-Triacetylphenothiazine

On the other hand, the use of phenothiazine, acetic anhydride, and aluminum chloride in carbon disulfide has been shown to give a di(ring-substituted)diacetylphenothiazine (108); later work has shown that this product is probably the 3,7-derivative (109).

This difference of orientation between phenothiazine and 10-acetylphenothiazine is not surprising, since carbazole has been shown to behave similarly in Friedel–Crafts reactions (129).

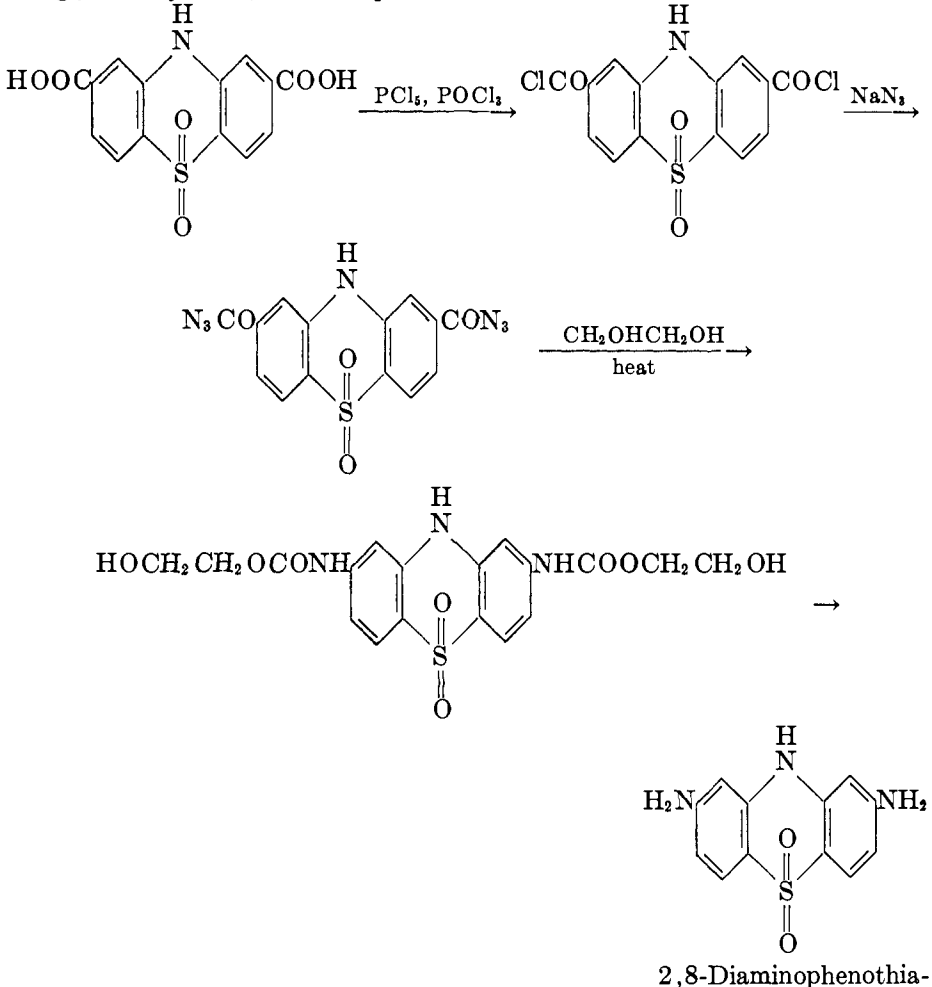
The Friedel–Crafts reaction also occurred in 58 per cent yield between 10-acetylphenothiazine and β-carbomethoxypropionyl chloride to form 2-succinylphenothiazine (4). 10-Acetylphenothiazine and succinic anhydride gave a 9 per cent yield of 2-succinylphenothiazine (4).

No alkylation of phenothiazine by the Friedel–Crafts method has been reported.

6. Miscellaneous nuclear substitution methods

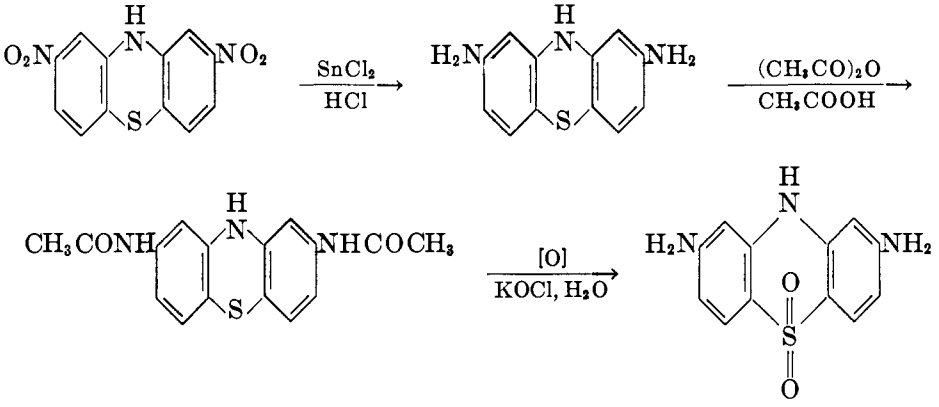
2,10-Diacetylphenothiazine was found to undergo the haloform reaction to give phenothiazine-2-carboxylic acid (4), which in turn was converted to its methyl and ethyl esters. These workers (4) also prepared the oxime of 2-acetylphenothiazine.

Similarly, 2,8,10-triacetylphenothiazine yielded phenothiazine-2,8-dicarboxylic acid and 2,8-diacetylphenothiazine 5-dioxide yielded phenothiazine-5-dioxide-2,8-dicarboxylic acid (115). This acid, in turn, underwent the Curtius rearrangement *via* the diacid chloride and diazide. The rearrangement could not be carried out *via* the isocyanate, but instead went through the urethan in ethylene glycol to yield 2,8-diaminophenothiazine 5-dioxide.



2,8-Diaminophenothiazine 5-dioxide

This compound was also obtained by the reduction of the 2,8-dinitrophenothiazine prepared by the ring-closure of 2-amino-2′-iodo-4,4′-dinitrodiphenyl sulfide and subsequent oxidation of the diacetamido compound by potassium hypochlorite.



2,8-Diaminophenothiazine 5-oxide

10-Methylphenothiazine readily formed 3-formyl-10-methylphenothiazine in 90 per cent yield by reaction with *N*-methylformanilide (25). Wolff–Kishner reduction of this compound gave 3,10-dimethylphenothiazine, which was identical with an authentic sample prepared by the 10-methylation of 3-methylphenothiazine.

10-Ethyl-3-iodophenothiazine underwent the Grignard reaction in an ether–benzene solution to give, subsequent to carbonation, a 76 per cent yield of 10-ethylphenothiazine-3-carboxylic acid (68). 10-Ethyl-4-iodophenothiazine 5-dioxide underwent rearrangement during amination with sodium amide to form 3-amino-10-ethylphenothiazine 5-dioxide (63).

Diazotization reactions of phenothiazine amines have varied in their success. Krishna and Jain (102) reported that 3-aminophenothiazine could be diazotized and the amino group removed. A successful Sandmeyer reaction was carried out with 3-amino-10-ethylphenothiazine to form 3-bromo-10-ethylphenothiazine (63), but a Sandmeyer reaction with 3-amino-10-methylphenothiazine was unsuccessful (57), as was an attempt to diazotize 7-amino-3-bromophenothiazine and remove the amino group (4). 3-Aminophenothiazine 5-oxide, when diazotized, coupled with resorcinol (98).

C. SUBSTITUTION OF THE AMINO HYDROGEN

Because of the widespread interest in 10-substituted phenothiazines, due to their therapeutic activity, much of the recent work on phenothiazine has been concerned with the replacement of the amino hydrogen. Three principal types of reagents have been used as alkylating agents: alcohols, sulfates, and halides. Aryl, acyl, and sulfonyl halides have been used to acylate the nitrogen.

1. Alkylation reactions

(a) Alcohols as alkylating agents

The first alkylations of phenothiazine to form 10-methyl- and 10-ethylphenothiazines were carried out by heating phenothiazine, the alkyl halide, and the corresponding alcohol in a sealed tube at 110–115°C. (14). It was later found (11) that the halide was unnecessary, and that the appropriate alcohol, a small amount of dry hydrogen chloride, and phenothiazine in a sealed tube yielded the methyl derivative in 60 per cent yield and the ethyl derivative in 35 per cent yield. The alcohols of higher molecular weight gave no reaction under these conditions. Refluxing a methanol solution of methyl iodide and phenothiazine for several days has been reported to give the 10-methyl derivative (44).

(b) Sulfates as alkylating agents

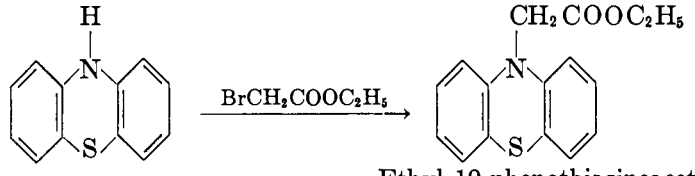
Methyl sulfate has also been shown to alkylate phenothiazine in 40 per cent yield, by refluxing a solution of phenothiazine in dioxane with methyl sulfate and anhydrous potassium carbonate for 24 hr. (64). 3-Methylphenothiazine was methylated in the 10-position with dimethyl sulfate in acetone containing sodium hydroxide (25). Phenothiazine was not, however, alkylated with diethyl sulfate (68).

(c) Halides as alkylating agents

In the alkylation of phenothiazine compounds by halides, it is generally necessary to use a basic condensing agent. Earlier workers used the alkali carbonates and copper powder as a catalyst, but more recent work indicates that sodium amide is the reagent of choice for alkyl halides in this reaction, although not for aryl halides.

10-Allyl-, 10-*n*-decyl, and 10-*n*-octadecylphenothiazines were prepared in yields of 62, 9, and 20 per cent, respectively, by heating the alkyl bromide, phenothiazine, sodium carbonate, and copper powder in xylene (66). The same authors found that direct heating of phenothiazine with a diethylaminopropyl halide or hydrohalide was unsuccessful.

Ethyl 10-phenothiazineacetate was prepared by heating a mixture of phenothiazine, ethyl bromoacetate, potassium carbonate, and copper powder (28).



Ethyl 10-phenothiazineacetate

Ethyl β-bromopropionate gave ethyl 10-phenothiazinepropionate. These esters were saponified to the free acids. 10-Phenothiazineacetic acid lost carbon dioxide on boiling to form 10-methylphenothiazine; the propionic acid derivative was stable under these conditions.

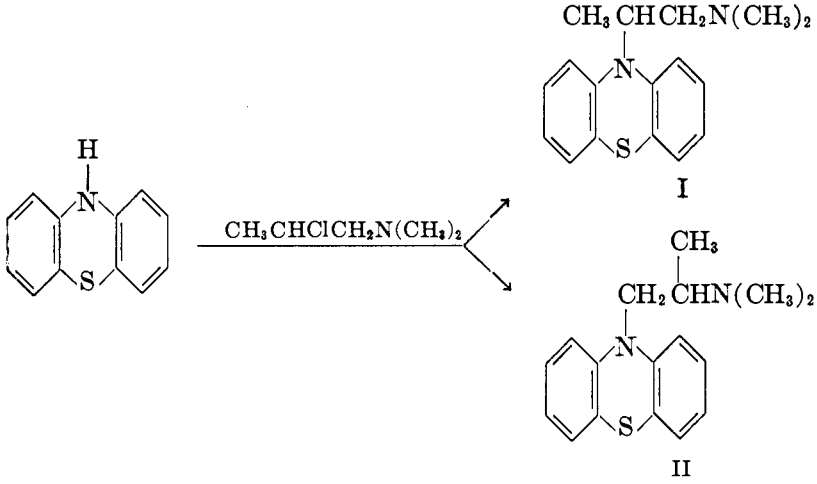
Aryl iodides have also been used as alkylating agents. Phenothiazine, iodobenzene, potassium carbonate, copper iodide, and bromobenzene gave 10-phenyl-

phenothiazine (6, 57). It was later shown that copper iodide could be replaced with advantageous results by copper bronze, and that bromobenzene was unnecessary. In this manner, a series of variously substituted 10-phenylphenothiazines (carbomethoxy, chloro, methoxy, methyl, nitro) were prepared from phenothiazine, the aryl iodide, potassium carbonate, and copper bronze in a high-boiling inert solvent (66, 68).

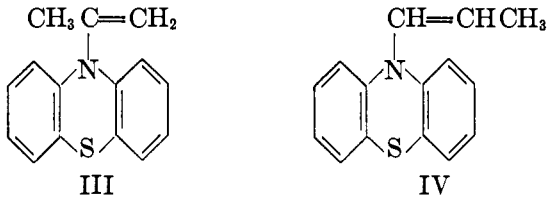
10-Ethyl- and 10-benzylphenothiazines were prepared by the reaction of ethyl bromide or benzyl chloride with 10-sodiophenothiazine, the latter prepared from phenothiazine and sodium amide (65). In the case of 10-ethylphenothiazine, the reaction proceeded more satisfactorily in liquid ammonia than in refluxing benzene. The procedure for the preparation of 10-ethylphenothiazine has been fur ther developed for 600-g. runs (63), and used to prepare 10-*n*-propyl, 10-isopropyl-, and 10-*p*-methoxybenzylphenothiazines.

Iodobenzene, however, did not react with 10-sodiophenothiazine (64).

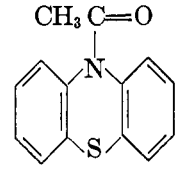
In alkylations involving alkylaminoalkyl halides with sodium amide and phenothiazine, rearrangement has been found, and in some cases isomers have been isolated. Charpentier (29) alkylated phenothiazine with 2-chloro-1-dimethylaminopropane in the presence of sodium amide, expecting to prepare 10-(1-dimethylamino-2-propyl)phenothiazine (I). He found, instead, that most of the product was actually 10-(2-dimethylamino-1-propyl)phenothiazine (II).



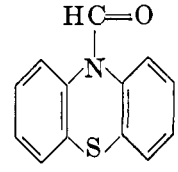
When the product (either I or II) was subjected to exhaustive methylation, an unsaturated compound was obtained, which might have had either structure III or structure IV.



If the unsaturated product had structure III, oxidation would give 10-acetylphenothiazine, whereas if it had structure IV, 10-formylphenothiazine would result.

III $\xrightarrow{\text{oxidation}}$ 

10-Acetylphenothiazine

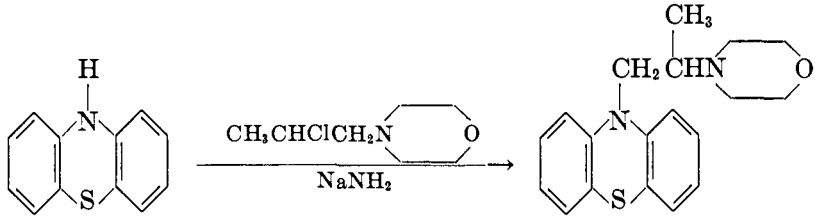
IV $\xrightarrow{\text{oxidation}}$ 

10-Formylphenothiazine

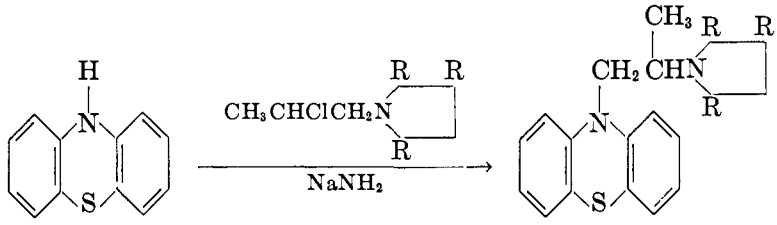
Since 10-formylphenothiazine was obtained, the alkylation was shown to have formed 2-dimethylamino-1-propylphenothiazine (II). Charpentier (29) also obtained the same compound from phenothiazine and 1-chloro-2-dimethylaminopropane.

This rearrangement of 2-chloro-1-dialkylaminopropanes is not unusual. In work on amidone (23, 100, 135, 138, 139, 140) it was shown that, under the influence of alkaline agents, alkylaminochloropropanes give rise to an intermediate cyclic ethylenimmonium ion, which may then rearrange to yield isomeric products.

Some 1-piperidyl- and 4-morphinolylalkyl derivatives of phenothiazine have been prepared by condensing the hydrochloride of 2-chloro-1-(1-piperidyl)propane and 2-chloro-1-(4-morpholinyl)propane with phenothiazine in the presence of 2 equivalents of sodium amide (39, 149). In the case of the chloropropanes, only one product was isolated and it was proved to be the rearranged product.

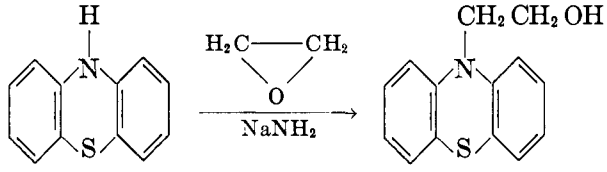


Phenothiazine has also been alkylated in good yield with variously substituted *N*-pyrrolidylethyl chlorides in the presence of sodium amide (132). These workers also used several 2-chloro-1-(1-pyrrolidyl)propanes as alkylating agents and assumed that they obtained the rearranged products, the 10-[2-(1-pyrrolidyl)-1-propyl]phenothiazines. They made no attempt to prove the structure of these compounds.



Other 10-dialkylaminoalkylphenothiazines have been prepared from phenothiazine and ring-substituted phenothiazines with sodium amide and dialkylaminoalkyl halides in solvents like xylene at high temperatures (31, 148).

Phenothiazine and its derivatives react with propylene or ethylene oxides in the presence of basic agents, such as sodium amide, sodium phenoxide, or lithium propionate, to give the corresponding 10-(2-hydroxyalkyl)phenothiazines (40).



10-(2-Hydroxyethyl)phenothiazine

Lithium amide has been used (167) with varying degrees of success in the preparation of 10-substituted phenothiazines.

10-Lithiophenothiazine, prepared from butyllithium and phenothiazine (66), reacted with various chloroalkyl *p*-toluenesulfonates to give the corresponding chloroalkylphenothiazines, which on treatment with secondary amines gave the corresponding 10-(dialkylaminoalkyl)phenothiazines. 10-(2-Chloroethyl)phenothiazine reacted with 2-(methylamino)ethanol to give 10-[2-(2-hydroxyethyl)-methylamino]ethylphenothiazine (38). 10-Lithiophenothiazine, from phenyllithium and phenothiazine, did not, however, react with benzyl chloride (65).

Grignard complexes of dialkylaminoalkyl halides have been shown to alkylate phenothiazine to yield 10-(dialkylaminoalkyl)phenothiazines (10).

The reaction of 2-(chloromethyl)imidazoline hydrochloride and phenothiazine in refluxing *o*-dichlorobenzene for 14 hr. gave 10-(2-imidazolylmethyl)phenothiazine hydrochloride (116). The same compound was also prepared from 10-cyanoethylphenothiazine, ethylenediamine, and hydrogen sulfide. 3-Methoxyphenothiazine underwent the same alkylation.

Phenothiazine undergoes cyanoethylation (145) to give β-(1-phenothiazyl)-propionitrile in 73 per cent yield.

The cyanoethylation reaction involving 2-trifluoromethylphenothiazine gave the propionitrile in 67 per cent yield (146).

2. Acylation reactions

The first acylation of phenothiazine, the formation of 10-acetylphenothiazine, was carried out by refluxing a solution of phenothiazine in acetic anhydride (14).

Other anhydrides which have been used to acylate phenothiazine include succinic anhydride (4) and phthalic anhydride (165). Pyridine is used as a catalyst in acylations with anhydrides (82).

Phenothiazine and its derivatives are readily acylated by acid chlorides in pyridine solution (82). In a similar manner, phenothiazine and its derivatives reacted with various haloacyl halides, in refluxing benzene or toluene, to give the corresponding 10-haloacylphenothiazines in good yield (41, 51). These, in turn, were treated with primary and secondary amines to give 10-aminoacylphenothiazines.

A number of 10-acylphenothiazines were prepared by heating equivalent amounts of the long-chain fatty acid chlorides and phenothiazine (58). 10-Acylphenothiazines have also been prepared by reacting the acid chloride with phenothiazine in dioxane with the addition of sodium carbonate (64).

Phenothiazine and 3,7-dinitrophenothiazine reacted with benzenesulfonyl chloride in pyridine to give the corresponding sulfonyl derivative (82). Likewise, 10-*p*-acetamidobenzenesulfonyl-, 10-*p*-nitrobenzenesulfonyl-, and 10-*p*-toluenesulfonylphenothiazines were prepared from the corresponding chlorides and phenothiazine (11, 90).

Benzoyl chloride reacted with 3-nitrophenothiazine 5-oxide to yield 10-benzoyl-3-nitrophenothiazine 5-oxide (82). Phenothiazine and ethyl chlorocarbonate yielded 10-carboethoxyphenothiazine (59). Phosgene with phenothiazine formed 10-chlorocarboxyphenothiazine (59).

D. MODIFICATION OF THE SULFIDE LINKAGE

The reactions involving the sulfur atom of phenothiazine may be divided into four broad classes: (*1*) those in which the sulfide linkage is oxidized either to the 5-oxide (sulfoxide) or to the 5-dioxide (sulfone); (*2*) those in which the sulfoxide or sulfone is reduced to the sulfide; (*3*) those in which the sulfur atom is removed; and (*4*) those in which a quaternary sulfur compound, called a phenothiazonium salt, is involved. The latter class of compounds is not discussed in this review.

1. Oxidation of the sulfide linkage to sulfoxides and sulfones

The sulfide linkage in phenothiazine may be oxidized by a number of oxidizing agents, the most common ones being potassium permanganate and hydrogen peroxide, although nitric acid, potassium hypochlorite, chromic anhydride, and sodium nitrite have been used.

Hot aqueous potassium permanganate solution oxidized 10-methylphenothiazine (15) and 10-ethylphenothiazine (11) to the sulfones in about 57 per cent yield. This reagent, however, did not oxidize the 10-acylated derivatives so easily, the 10-*p*-toluenesulfonyl derivative giving the sulfoxide and the 10-acetyl- and 10-*p*-acetamidobenzenesulfonyl derivatives not being oxidized (11).

When acetone with a little sulfuric acid was used as the reaction medium 10-methylphenothiazine on oxidation by permanganate gave only a 45 per cent yield of the sulfoxide and very little sulfone (6). However, in acetone and acetic acid, permanganate oxidized 10-benzylphenothiazine to the sulfone (57). In cold

acetone 10-(1-propenyl)phenothiazine was oxidized by permanganate to 10-formylphenothiazine without any oxidation of the sulfur atom (32).

In 75 per cent acetic acid potassium permanganate oxidized ethyl 10-phenothiazinecarboxylate to the sulfone in 83 per cent yield (11). Aqueous permanganate oxidized 10-phenylphenothiazine in chloroform to the sulfone (57).

When phenothiazine in acetone was treated with 30 per cent hydrogen peroxide and a small amount of sodium ethoxide, and the mixture was permitted to stand for 10 days, a small amount of phenothiazine 5-dioxide was obtained (6). Later workers were unable to duplicate these results (131). Only small quantities of 10-methylphenothiazine 5-oxide were obtained when a solution of 10-methylphenothiazine and hydrogen peroxide was permitted to stand for 3 weeks (6). Neither the 10-*p*-toluenesulfonyl nor the 10-*p*-acetamidobenzenesulfonyl derivative of phenothiazine could be oxidized with hydrogen peroxide in acetone (11).

In ethanol as a solvent, in contrast to this behavior in acetone, hydrogen peroxide easily oxidized many phenothiazine derivatives to the sulfoxides (64, 66, 87, 93), and phenothiazine itself was oxidized either to the sulfoxide in the presence of potassium hydroxide (64) or to the sulfone (131).

Hot glacial acetic acid has also been used successfully as a solvent in hydrogen peroxide oxidations. 2,8,10-Triacetylphenothiazine gave 2,8-diacetylphenothiazine 5-dioxide (115). Many other nuclear-substituted and 10-substituted phenothiazines were readily converted to the corresponding sulfones by the action of hydrogen peroxide in hot glacial acetic acid (63, 64, 146).

With hydrogen chloride in ethanol, hydrogen peroxide oxidized and chlorinated phenothiazine to a trichlorophenothiazine 5-oxide (22).

Treatment with concentrated nitric acid (17, 66, 99) or with nitric acid in glacial acetic acid (64) resulted in both nitration and oxidation, the sulfoxide being formed. In the case of a tetranitrophenothiazonium hydroxide, concentrated nitric acid gave the sulfone (6).

Potassium hypochlorite in acetic acid oxidized 2,8-diacetamido-10-acetylphenothiazine in poor yield (115). Chromic anhydride in acetic acid converted 3,7-dinitrophenothiazine 5-oxide to the dioxide (34).

2. Reduction of the sulfoxides and sulfones

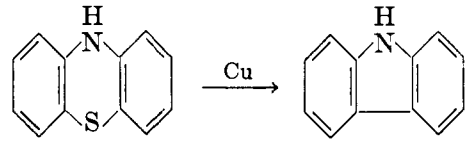
The reduction of 3,7-dinitrophenothiazine 5-oxide to 3,7-dinitrophenothiazine has been effected by ethanol and sulfuric acid (94). Stannous chloride in hydrochloric acid reduced 3-nitrophenothiazine 5-oxide and 3,7-dinitrophenothiazine 5-oxide to the corresponding aminophenothiazines (99). On the other hand, both stannous chloride in hydrochloric acid and ammonium sulfide in ammonia reduced only the nitro groups and not the sulfone in converting 3,7-dinitrophenothiazine 5-dioxide into 3,7-diaminophenothiazine 5-dioxide (34).

Hydrogen chloride has served as both a reducing and a chlorinating agent in the conversion of several 5-oxides into chlorophenothiazines. The position of the chlorine atom is usually 3 or 7. Examples include phenothiazine 5-oxide, 10-methylphenothiazine 5-oxide, 3,7-dinitrophenothiazine 5-oxide, 3-nitrophenothiazine 5-oxide (126), and 10-ethylphenothiazine 5-oxide (63).

3. Removal of the sulfur atom

In one of the steps in his classic proof of the structure of phenothiazine, Bernthsen (16) converted phenothiazine into phenylacridine by heating it with benzoic acid and zinc chloride (see page 799).

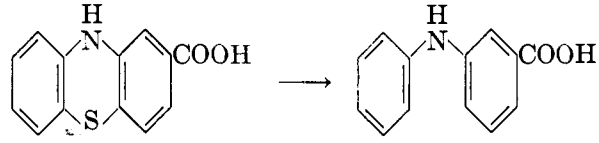
Phenothiazine (72), as well as its derivatives (29), yielded the corresponding carbazoles on heating with copper.



Phenothiazine Carbazole

Phenothiazine underwent berginization in the presence of molybdenum oxide to give diphenylamine, aniline, and benzene (125). In dioxane, at 230°C. and high pressure, with cobalt sulfide as a catalyst, hydrogen and phenothiazine gave diphenylamine and *o*-mercaptodiphenylamine (143).

Raney nickel has been used to remove sulfur from the phenothiazine nucleus. Thus, phenothiazine gave diphenylamine (141) and 2-carboxyphenothiazine gave *m*-carboxydiphenylamine (4).



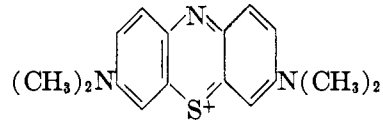
2-Carboxyphenothiazine *m*-Carboxydiphenylamine

Hydriodic acid, in the same manner, reduced 10-ethyl- and 10-phenylphenothiazine-4-carboxylic acids to *m*-carboxydiphenylamine and *m*-carboxytriphenylamine, respectively (66).

VI. Phenothiazine Drugs

Although a detailed and complete discussion of the physiological properties of phenothiazine and its derivatives is not within the scope of this review, the increasing importance of these compounds as drugs, particularly the 10-substituted derivatives, makes it desirable that brief mention be made of the more important drugs derived from phenothiazine.

Historically, it is significant that methylene blue, a phenothiazine derivative, was the first synthetic antimalarial (75).



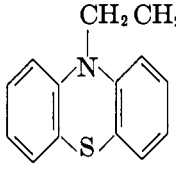
Methylene blue

Phenothiazine itself has been shown to be a good antihelmintic (56), urinary antiseptic (43, 154), and antituberculostatic compound (60). The chemotherapy of phenothiazine as an antihelmintic, both in animals and in man, and a very excellent discussion on the toxicity of phenothiazine in animals is given by Findlay (56).

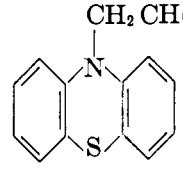
Five of the most important phenothiazine drugs are the following: 10-(2-dimethylaminoethyl)phenothiazine, called RP3015; 10-(2-dimethylamino-1-propyl)phenothiazine, called phenergan or RP3277; 10-(2-diethylaminoethyl)phenothiazine, called diparcol; 2-chloro-10-dimethylaminoisopropylphenothiazine, called RP4560 or chloropromazine; and 10-*N*-pyrrolidylethylphenothiazine, called pyrrolazote. The compounds are used as their hydrochlorides.

Quaternary ammonium derivatives of many of these and related derivatives have shown physiological activity (30).

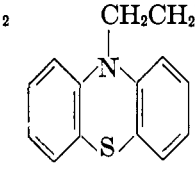
It is of interest to note that Gilman and Shirley in 1944 prepared a series of 10-dialkylaminoalkylphenothiazines (66), but tested them only for antimalarial activity; the compounds were found to be ineffective in this respect. Halpern (76, 78), however, found that these types of compounds had considerable antihistaminic activity, particularly RP3015 and RP3277. They were also found to have considerably less toxicity than any other reported antihistamine (77, 78).



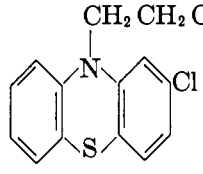
RP3015



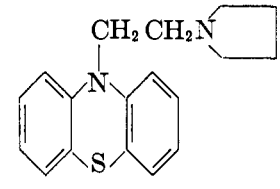
Phenergan or RP3277



Diparcol



Chloropromazine



Pyrrolazote

1. RP3015

RP3015, in addition to its antihistaminic activity, showed a local anesthetic activity twice that of cocaine (79) and five times that of procaine (81). It has, however, no effect in Parkinson's disease (20, 106).

2. Phenergan or RP3277

Phenergan, as used in most experiments, was found (32) to be a mixture of 10-(2-dimethylamino-1-propyl)phenothiazine, also called promethazine, and 10-(1-dimethylamino-2-propyl)phenothiazine, the former being present in the larger amount and also being the more effective drug.

Phenergan, in addition to its antihistaminic activity, has twice the local anes-

thetic activity of cocaine (79). It was found to be effective in the prevention of acute edema of the lungs in rats caused by chloropicrin (77). When anesthetized cats were injected with phenergan, there was an immediate fall in the blood pressure, which was proportional to the amount injected (70). Phenergan is the most antibiotic of any of the antihistamines (105). Phenergan partially inhibited the action of trypsin and papain on gelatin, but had no effect on pepsin (104). Phenergan, when injected into rabbits, caused inoculated vaccine virus to spread rapidly throughout their bodies (19).

In humans, phenergan has shown side effects of drowsiness, lassitude, lightheadedness, and aching limbs (3).

3. Diparcol

Diparcol has been shown to suppress the bronchospasms produced in guinea pigs by histamine, acetylcholine, and nicotine (136). It did not, however inhibit the effect of histamine on the heart (7). Diparcol also reduced considerably the action of large doses of nicotine on the heart, the arterial pressure, and the respiratory and nerve centers of various animals.

However, its most important use has been in the treatment of Parkinson's disease, in which it has been shown to be clinically effective (20, 24). Diparcol, in a manner similar to diisopropyl fluorophosphate, exerted a selective inhibiting action on pseudocholinesterase, without exerting an appreciable effect on cholinesterase (27, 71, 80, 83), while on the other hand it completely antagonized the effects of diisopropyl fluorophosphate. More complete discussions of the pharmacological properties of diparcol are given in two papers (81, 83).

4. Chloropromazine

Chloropromazine was shown to be very effective (61) in suppressing the nausea and vomiting caused by a wide variety of clinical conditions, such as carcinomatosis, labyrinthitis, lymphomatosis, and uremia. It was also found effective in controlling the nausea and vomiting caused by the administration of antabuse to patients under alcohol and that produced by aureomycin, folic acid antagonist, codeine, meperidine, methadone, morphine, nitrogen mustards, protoveratrine, terramycin, and urethan therapy. The only side effects observed were dryness of the mouth, occasional mild sedation, and a mild transient attack of faintness, palpitation, and flushing of the face. A review of its physiological properties has been published (35).

5. Pyrrolazote

Pyrrolazote has been found to have very good antihistaminic properties (132). Its physiological properties have been described (159).

VII. Oxidized Forms of Phenothiazine

While this review does not cover the oxidized (quinonoid) forms of phenothiazine, the ease with which phenothiazine derivatives are oxidized, not to the sulfoxide nor the sulfone but apparently to a quinonoid structure, makes it de-

sirable that the reader who wishes further information in this important field be referred to the review by Meyer and Jacobsen (112) and to the excellent papers by Michaelis, Granick, and Schubert (74, 113, 114) and by Houston and coworkers (87, 88).

VIII. Phenothiazine and its Compounds as Antioxidants

One of the most important industrial applications of phenothiazine and its compounds is their use as antioxidants in preventing oxidative changes in polyethylene oils (119). There are numerous applications for high-temperature antioxidants, such as additives to greases for silicone-clad motors and generators and as lubricants for gas turbines and turbojet engines. Phenothiazine and its compounds have shown a high order of inhibition (120, 146, 163).

The author wishes to acknowledge his indebtedness to his colleagues, Dr. Ivar Cooke and Dr. Herman Zittel, for their aid in reviewing this article and a portion of the literature; to the Research Corporation and the National Cancer Institute for financial grants for studies on phenothiazine; and to Dr. Henry Gilman, his former professor, for inspiration and encouragement.

Special thanks are also due to his senior assistants, Don Roper and Frank Robinson, for aid in reviewing the literature.

IX. References

(1) Ackermann, F.: German patent 222,879; Friedlander **10**, 144 (1911).
(2) Ackermann, F.: German patent 224,348; Chem. Zentr. **1911**, I, 1080.
(3) Bain, W. A., Hellier, F. F., and Worin, R. O. P.: Lancet **255**, 964 (1948).
(4) Baltzly, R., Harfenist, M., and Webb, F. J.: J. Am. Chem. Soc. **68**, 2673 (1946).
(5) Barnes, R. B., Gore, R. C., Stafford, R. W., and Williams, V. Z.: Anal. Chem. **20**, 402 (1948).
(6) Barnett, E. DeB., and Smiles, S.: J. Chem. Soc. **97**, 188 (1910).
(7) Beck, I. T., Frommel, E., Favre, M., and Vallette, F.: Arch. intern. pharmacodynamie **78**, 613 (1949); Chem. Abstracts **43**, 7129 (1949).
(8) Beeler, E. C.: Bull. Natl. Formulary Comm. **10**, 84 (1942).
(9) Bennett, G. M.: J. Chem. Soc. **1953**, 4192.
(10) Berg, S. C., and Ashley, J. N.: U. S. patent 2,607,773; Chem. Abstracts **47**, 6989 (1953).
(11) Bernstein, H., and Rothstein, L.: J. Am. Chem. Soc. **66**, 1886 (1944).
(12) Bernthsen, A.: Ber. **16**, 2896 (1883).
(13) Bernthsen, A.: Ann. **230**, 73–212 (1885).
(14) Bernthsen, A.: Ann. **230**, 88, 93, 95 (1885).
(15) Bernthsen, A.: Ann. **230**, 91 (1885).
(16) Bernthsen, A.: Ann. **230**, 100 (1885).
(17) Bernthsen, A.: Ann. **230**, 100–108 (1885).
(18) Bernthsen, A.: Ber. **45**, 2012 (1912).
(19) Borski, G.: Compt. rend. soc. biol. **143**, 1568 (1949).
(20) Bovet, D., Durel, P., and Longo, V.: Compt. rend. soc. biol. **144**, 514 (1950).
(21) Bovet, D., Fournel, J., and Charpentier, P.: Thérapie **2**, 115 (1947); Chem. Abstracts **42**, 5116 (1948).
(22) Brady, O. L., and Smiles, S.: J. Chem. Soc. **97**, 1559 (1910).
(23) Brode, W. R., and Hill, M. W.: J. Am. Chem. Soc. **69**, 724 (1947).

(24) BURGER, A.: *Medicinal Chemistry*, Vol. I, p. 456. Interscience Publishers, Inc., New York (1951).
(25) BUU-HOÏ, NG. PH., AND HOÁN, N. G.: J. Chem. Soc. **1951**, 1834.
(26) CAMPBELL, F. L., SULLIVAN, W. N., SMITH, L. E., AND HALLER, H. L.: J. Econ. Entomol. **27**, 1176 (1934).
(27) CASLET, H.: Arch. intern. pharmacodynamie **82**, 155 (1950); Chem. Abstracts **44**, 7983 (1950).
(28) CAUQUIL, G., AND CASSADEVALL, A.: Compt. rend. **225**, 578 (1947).
(29) CHARPENTIER, P.: Compt. rend. **225**, 306 (1947).
(30) CHARPENTIER, P.: U. S. patent 2,480,355; Chem. Abstracts **44**, 1145 (1950).
(31) CHARPENTIER, P.: U. S. patent 2,319,886; Chem. Abstracts **45**, 673 (1951).
(32) CHARPENTIER, P., AND DUCROT, R.: Compt. rend. **232**, 415 (1951).
(33) CHARPENTIER, P., GAILLOT, P., JACOB, R., GAUDECHON, J., AND BUISSON, P.: Compt. rend. **235**, 59 (1952).
(34) CIOCCA, B., AND CANONICA, L.: Boll. ist. sieroterap. milan. **23**, 81 (1944); Chem. Abstracts **40**, 3119 (1946).
(35) COURVOISIER, S., FOURNEL, J., DUCROT, R., KOLSKY, M., AND KOETSCHET, P.: Arch. intern. pharmacodynamie **92**, 305 (1953).
(36) CULVENOR, C., DAVIES, W., AND HEATH, N. S.: J. Chem. Soc. **1949**, 278.
(37) CUPPLES, H. L.: Ind. Eng. Chem., Anal. Ed. **14**, 53 (1942).
(38) CUSIC, J. W.: U. S. patent 2,512,520; Chem. Abstracts **44**, 8963 (1950).
(39) DAHLBOM, R.: Acta Chem. Scand. **3**, 247 (1949).
(40) DAHLBOM, R.: Swedish patent 129,843; Chem. Abstracts **45**, 5193 (1951).
(41) DAHLBOM, R., AND EKSTRAND, T.: Acta Chem. Scand. **5**, 102 (1951).
(42) DECOURT, P.: Bull. acad. natl. med. **114**, 632 (1950); Chem. Abstracts **45**, 3942 (1951).
(43) DE EDS, F., AND THOMAS, J. O.: J. Parasitol. **24**, 363 (1942).
(44) DELANEY, B. P.: Private communication to H. Bernstein (11).
(45) DESAI, R. D.: J. Indian Inst. Sci. **1**, 235 (1924); Chem. Abstracts **19**, 2645 (1925).
(46) DUCROT, R., AND DECOURT, P.: Compt. rend. soc. biol. **144**, 908 (1950).
(47) DUVAL, R.: Anal. Chem. Acta **3**, 21 (1949); Chem. Abstracts **43**, 8299 (1949).
(48) ECKERT, A., AND STEINER, K.: Monatsh. Chem. **35**, 1153 (1914).
(49) EDDY, C. W., AND DE EDS, F.: Food Research **2**, 305 (1937).
(50) EISCH, J.: Unpublished studies, mentioned in reference 63.
(51) EKSTRAND, T.: Swedish patent 127,566; Chem. Abstracts **45**, 1886 (1951).
(52) EVANS, W. J., AND SMILES, S.: J. Chem. Soc. **1935**, 181.
(53) EVANS, W. J., AND SMILES, S.: J. Chem. Soc. **1935**, 1263.
(54) FARBENINDUSTRIE I.-G.: German patent 582,268; Chem. Abstracts **27**, 5196 (1933).
(55) FARBENINDUSTRIE I.-G.: British patent 420,444; Chem. Abstracts **29**, 3530 (1935).
(56) FINDLAY, G. M.: *Recent Advances in Chemotherapy*, 3rd edition, Vol. I, p. 124. The Blakiston Company, Philadelphia (1950).
(57) FINZI, C.: Gazz. chim. ital. **62**, 175 (1932); Chem. Abstracts **26**, 4338 (1932).
(58) FORD, G. M.: Doctoral Dissertation, Iowa State College, 1937.
(59) FRAENKEL, N.: Ber. **18**, 1845 (1885).
(60) FREEDLANDER, B. L.: Proc. Soc. Exptl. Biol. Med. **57**, 106 (1944).
(61) FRIEND, D. G., AND CUMMINS, J. F.: J. Am. Med. Assoc. **153**, 481 (1953).
(62) GEIGER, L. M., AND BECK, C. N.: U. S. patent 2,433,658; Chem. Abstracts **42**, 1974 (1948).
(63) GILMAN, H., INGHAM, R. K., CHAMPAIGNE, J. F., JR., DIEHL, J. W., AND RANCK, R. O.: J. Org. Chem. **19**, 560 (1954).
(64) GILMAN, H., AND NELSON, R. D.: J. Am. Chem. Soc. **75**, 5422 (1953).
(65) GILMAN, H., NELSON, R. D., AND CHAMPAIGNE, J. F., JR.: J. Am. Chem. Soc. **74**, 4205 (1952).
(66) GILMAN, H., AND SHIRLEY, D. A.: J. Am. Chem. Soc. **66**, 888 (1944).
(67) GILMAN, H., SHIRLEY, D. A., AND VAN ESS, P. R.: J. Am. Chem. Soc. **66**, 626 (1944).

(68) GILMAN, H., VAN ESS, P. R., AND SHIRLEY, D. A.: J. Am. Chem. Soc. **66**, 1216 (1944).
(69) GILMAN, H., ZAREMBER, I., AND BEEL, J. A.: J. Am. Chem. Soc. **74**, 3177 (1952).
(70) GLANZMANN, S., AND SALVA-MIQUEL, J. A.: Acta Allergol. **2**, 26 (1949); Chem. Abstracts **43**, 7584 (1949).
(71) GORDON, J. J.: Nature **162**, 146 (1948).
(72) GOSKE, A.: Ber. **20**, 232 (1887).
(73) GRANICK, S., AND MICHAELIS, L.: J. Am. Chem. Soc. **69**, 2982 (1947).
(74) GRANICK, S., MICHAELIS, L., AND SCHUBERT, M. P.: J. Am. Chem. Soc. **62**, 1802 (1940).
(75) GUTTMAN, P., AND EHRLICH, P.: Berlin. klin. Wochschr. **28**, 593 (1891); Chem. Zentr. **1892**, **I**, 221.
(76) HALPERN, B. N.: Compt. rend. soc. biol. **140**, 363 (1946).
(77) HALPERN, B. N., AND CRUCHAUD, S.: Compt. rend. **225**, 1194 (1947).
(78) HALPERN, B. N., AND DUCROT, R.: Compt. rend. soc. biol. **140**, 361 (1946).
(79) HALPERN, B. N., PERRIN, G., AND DEWS, P.: Compt. rend. soc. biol. **140**, 363 (1946).
(80) HAWKINS, R. D., AND MENDEL, B.: Biochem. J. **44**, 260 (1949).
(81) HAZARD, R., CORTEGGIANI, E., AND CORNEC, A.: Compt. rend. soc. biol. **143**, 908 (1949).
(82) HAZLET, S. E., AND RODERICK, E. E.: J. Am. Chem. Soc. **67**, 496 (1945).
(83) HEYMANS, C., ESTABLE, J. J., AND DE BONNEVEAUX, S. C.: Arch. intern. pharmacodynamie **79**, 123 (1949); Chem. Abstracts **43**, 7129 (1949).
(84) HODGSON, H., DODGSON, D., AND SMITH, E.: J. Chem. Soc. **1948**, 1104.
(85) HODGSON, H., AND MARSDEN, A.: J. Soc. Dyers Colourists **60**, 210 (1944).
(86) HOLZMANN, C.: Ber. **21**, 2069 (1888).
(87) HOUSTON, D. F., KESTER, E. B., AND DE EDS, F.: J. Am. Chem. Soc. **71**, 3816 (1949).
(88) HOUSTON, D. F., KESTER, E. B., AND DE EDS, F.: J. Am. Chem. Soc. **71**, 3819 (1949).
(89) IDSON, B.: Chem. Revs. **47**, 351 (1950).
(90) JENSEN, K., POSSING, B., AND SCHMITH, K.: Dansk Tidsskr. Farm. **15**, 191 (1941); Chem. Abstracts **38**, 1482 (1944).
(91) KEHRMANN, F.: Ann. **322**, 54 (1902).
(92) KEHRMANN, F., AND DARDEL, J. H.: Ber. **55B**, 2346 (1922).
(93) KEHRMANN, F., AND DISERENS, L.: Ber. **48**, 318 (1915).
(94) KEHRMANN, F., AND NOSSENKO, O.: Ber. **46**, 2809 (1913).
(95) KEHRMANN, F., AND RINGER, F.: Ber. **46**, 3014 (1913).
(96) KEHRMANN, F., AND SCHILD, L.: Ber. **32**, 2605 (1899).
(97) KEHRMANN, F., AND STEINBERG, J.: Ber. **44**, 3011 (1911).
(98) KEHRMANN, F., AND VESSELY, O.: Ann. **322**, 54 (1902).
(99) KEHRMANN, F., AND ZYBS, P.: Ber. **52B**, 130 (1919).
(100) KERWIN, J. F., ULLYOT, G. E., FUSON, R. C., AND LUKLE, C. L.: J. Am. Chem. Soc. **69**, 2961 (1947).
(101) KNOEVENAGEL, E.: J. prakt. Chem. **89**, **2** (1914).
(102) KRISHNA, S., AND JAIN, M. S.: Proc. 15th Indian Sci. Cong. **1928**, 153; Chem. Abstracts **25**, 3001 (1931).
(103) LAUTH, C.: Ber. **9**, 1035 (1876).
(104) LEDUC, J. R.: Rev. can. biol. **8**, 439 (1949).
(105) LEDUC, J. R.: Rev. can. biol. **8**, 543 (1949).
(106) LONGO, V. G., AND BOVET, D.: Farm. sci. e tec. (Pavia) **4**, 515 (1949); Chem. Abstracts **44**, 1611 (1950).
(107) MARAL, R., CARRAX, M., AND BLAUDIN, A.: Compt. rend. soc. biol. **144**, 136 (1950).
(108) MASSIE, S. P.: Iowa State Coll. J. Sci. **21**, 74 (1946).
(109) MASSIE, S. P.: Unpublished observations.
(110) MATSUMURA, K.: J. Am. Chem. Soc. **52**, 3199 (1930).
(111) METCALF, R. L.: Chemistry Biology Coordination Center, National Research Council, Washington, D. C., Review No. 1, 84 pp. (1948).

(112) MEYER, V., AND JACOBSEN, P.: *Lehrbuch der organischen Chemie*, Vol. 2, part 3, p. 1490. Veit and Co., Leipzig (1920).
(113) MICHAELIS, L., GRANICK, S., AND SCHUBERT, M. P.: J. Am. Chem. Soc. **63**, 351 (1941).
(114) MICHAELIS, L., SCHUBERT, M. P., AND GRANICK, S.: J. Am. Chem. Soc. **62**, 204 (1940).
(115) MICHELS, J. G., AND AMSTUTZ, E. D.: J. Am. Chem. Soc. **72**, 888 (1950).
(116) MIESCHER, K., AND MARXER, A.: U. S. patent 2,485,212; Chem. Abstracts **44**, 2572 (1950).
(117) MITSUGI, R., BEYESCHLAG, H., AND MOHLAU, R.: Ber. **43**, 927 (1910).
(118) MOHLAU, R., BEYESCHLAG, H., AND KOHRES, H.: Ber. **45**, 136 (1912).
(119) MURPHY, C. M., RAINER, H., AND SMITH, N. L.: Anal. Chem. **42**, 2479 (1950).
(120) MURPHY, C. M., AND SANDERS, C. E.: Petroleum Refiner **26**, 479 (1947).
(121) *National Formulary*, Vol. IX, p. 81. American Pharmaceutical Association, Washington (1950).
(122) NELSON, R. D.: Doctoral Dissertation, Iowa State College, 1951.
(123) NIEDERL, J. B.: U. S. patent 2,483,838; Chem. Abstracts **44**, 2035 (1950).
(124) OLIVIER, S. C. J., AND COMBE, W. P.: Rec. trav. chim. **69**, 526 (1950).
(125) ORLOW, N. A., BURD, N. I., AND SSUKATSCHEWA, W. D.: Ber. **64B**, 2631 (1931).
(126) PAGE, H. J., AND SMILES, S.: J. Chem. Soc. **97**, 1115 (1910).
(127) PATTERSON, A. M., AND CAPELL, L. T.: *The Ring Index*, American Chemical Society Monograph Series, No. 84, p. 252. Reinhold Publishing Corporation, New York (1940).
(128) PAYFER, R., AND MARSHALL, C. V.: J. Assoc. Offic. Agr. Chemists **28**, 429 (1945).
(129) PLANT, S. G. P., ROGERS, K. M., AND WILLIAMS, S. B. C.: J. Chem. Soc. **1935**, 741.
(130) POLLAK, J., RIESZ, E., AND KAHANE, Z.: Monatsh. Chem. **49**, 213 (1928).
(131) PUMMERER, R., AND GASSNER, S.: Ber. **46**, 2322 (1913).
(132) REID, W. R., JR., WRIGHT, J. B., KOLLOFF, H. G., AND HUNTER, J. H.: J. Am. Chem. Soc. **70**, 3100 (1948).
(133) ROE, A., MONTGOMERY, J., HOYLE, V., AND VARNELL, W. A.: Abstracts of Papers Presented at the Southern and Southwestern Regional Meeting of the American Chemical Society, New Orleans, Louisiana, December, 1953.
(134) ROMANO, G.: Farm. sci. e tec. (Pavia) **4**, 25 (1948); Chem. Abstracts **43**, 4774 (1949).
(135) ROSS, S. D.: J. Am. Chem. Soc. **69**, 2982 (1947).
(136) SCHAEPDRYVER, A. DE: Arch intern. pharmacodynamie **82**, 207 (1950); Chem. Abstracts **44**, 7983 (1950).
(137) SCHOLL, R., AND SEER, C.: Ber. **44**, 1233 (1911).
(138) SCHULTZ, E. M., ROBB, C. M., AND SPRAGUE, J. M.: J. Am. Chem. Soc. **69**, 188 (1947).
(139) SCHULTZ, E. M., ROBB, C. M., AND SPRAGUE, J. M.: J. Am. Chem. Soc. **69**, 2454 (1947).
(140) SCHULTZ, E. M., AND SPRAGUE, J. M.: J. Am. Chem. Soc. **70**, 48 (1948).
(141) SHAH, K. H., TILAK, B. D., AND VENKATARAMAN, K.: Proc. Indian Acad. Sci. **28A**, 142 (1948); Chem. Abstracts **44**, 3958 (1950).
(142) SHIRLEY, D. A.: Doctoral Dissertation, Iowa State College, 1943.
(143) SIGNAIGO, F. K.: U. S. patent 2,402,686; Chem. Abstracts **40**, 5767 (1946).
(144) SMITH, L. E., AND NELSON, O. A.: J. Am. Chem. Soc. **64**, 461 (1942).
(145) SMITH, N. L.: J. Org. Chem. **15**, 1125 (1950).
(146) SMITH, N. L.: J. Org. Chem. **16**, 415 (1951).
(147) SMITH, P. A. S., BROWN, B. B., PITNEY, R. K., AND REINISCH, R. F.: J. Am. Chem. Soc. **75**, 6335 (1953).
(148) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 608,208; Chem. Abstracts **43**, 2647 (1949).
(149) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 632,277; Chem. Abstracts **44**, 5399 (1950).
(150) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 204,521; Chem. Abstracts **35**, 2337 (1941).

(151) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patents 209,500, 209,501, 209,502; Chem. Abstracts **35**, 4007 (1941).
(152) STEWART, V. E.: J. Assoc. Offic. Agr. Chemists **30**, 681 (1947).
(153) TAUBER, E.: Ber. **24**, 197 (1891).
(154) THOMAS, J. O.: J. Pharmacol. Exptl. Therap. **64**, 280 (1938).
(155) TOMLINSON, M. L.: J. Chem. Soc. **1936**, 1607.
(156) ULMANN, F., ENGL, G., WOSNESSENKY, N., KUHN, E., AND HERPE, E.: Ann. **366**, 79 (1909).
(157) UNGER, O., AND HOFFMAN, K.: Ber. **29**, 1362 (1896).
(158) VALLERY-RADOT, P., HAMBURGER, J., AND HALPERN, B. N.: Presse méd. **55**, 661 (1947); Chem. Abstracts **43**, 3525 (1949).
(159) VANDERBROOK, M. J., OLSON, K. J., RICHMOND, M. R., AND KUIZENEA, M. H.: J. Pharmacol. Exptl. Therap. **94**, 197 (1948).
(160) VAN ESS, P. R.: Doctoral Dissertation, Iowa State College, 1936.
(161) VENKATARAMAN, K.: *The Chemistry of Synthetic Dyes*, Vol. II, p. 791. Academic Press, Inc., New York (1952).
(162) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1932**, 2774.
(163) WEST, H. L.: J. Inst. Petroleum **34**, 774 (1948).
(164) WIGHT, C. F., AND SMILES, S.: J. Chem. Soc. **1935**, 340.
(165) WINNEK, P. S., AND FAITH, H. E.: U. S. patent 2,461,460; Chem. Abstracts **43**, 3853 (1949).
(166) WINTER, C. A.: J. Pharmacol. Exptl. Therap. **94**, 7 (1948).
(167) WRIGHT, J. B., LINCOLN, E. H., HEINZELMAN, R. V., AND HUNTER, J. H.: J. Am. Chem. Soc. **72**, 3536 (1950).

X. APPENDIX: TABLES OF DERIVATIVES

In tables 1 to 8 are listed the melting points of the simple phenothiazine derivatives.

TABLE 1

Derivatives of phenothiazine containing a substituent in one ring

Substituent	Melting Point	References
	°C.	
1-Acetamido-	174	(94)
2-Acetyl-	192–193	(4)
2-Acetyl-oxime-	242–243	(4)
2-Carboethoxy-	152–152.5	(4)
1-Carbomethoxy-	113–113.5	(67)
2-Carbomethoxy-	167–168	(4)
3-Carbophenoxy-	202–203	(131)
1-Carboxy-	264–265	(67)
2-Carboxy-	276–277 (dec.)	(4)
3-Carboxymethoxy-	217–218	(4)
2-Chloro-	196–197	(33)
3-Chloro-	199	(53)
4-Chloro-	116	(33)
3-Dodecyloxy-	101–103	(87)
3-Fluoro-	176–177	(146)
3-Hexadecyloxy-	101.5–103	(87)
3-Hydroxy-	172–174	(87)
3-Isopropoxy-	123–123.7	(87)
2-Methoxy-	179–180	(33)
3-Methoxy-	158–159	(66, 94)
	163	(131)
2-Methyl-	187–188	(33)
3-Methyl-	166–168	(66)
4-Methyl-	114–118	(33)
1-Nitro-	111	(94)
3-Nitro-	218	(52, 94, 102)
2-Succinyl-	251–252	(4)
2-Trifluoromethyl-	188–189	(146)

TABLE 2

Derivatives of phenothiazine containing substituents in two rings

Substituents	Melting Point	References
	°C.	
2-Bromo-7-amino-	237–238	(4)
2-Bromo-7-nitro-	224	(4)
1 (or 4)-Carboxy-3-methoxy-	203–204	(4)
3-Carboxy-1-nitro-	316	(156)
3-Chloro-7-nitro-	268	(94)
2,8-Diacetyl-	249–251	(115)
3?,7?-Diacetyl-	153–254	(108)
2,8-Dicarboxy-	Above 360 (dec.)	(115)
1,3-Dichloro-	225–227	(157)
3,7-Dichloro-	222	(157)
1,3-Dinitro-	188	(95, 96, 117, 118)
2,8-Dinitro-	355–360	(115)
3,7-Dinitro-	276	(94)
1,3,7,9-Tetrachloro-	235	(94, 157)
1,3,7-Trinitro-	214	(95)
2-Trifluoromethyl-8-methyl-	227–228	(145)

TABLE 3

10-Alkyl derivatives of phenothiazine

Substituents	Melting Point	References
	°C.	
10-Allyl-	187-195/1 mm.*	(66)
10-Benzyl-	90-92	(45, 65, 69)
10-(2-Carboxyethyl)-	162-163	(28, 145)
10-(β-Chloroethyl)-	97-98	(66)
10-(γ-Chloropropyl)-	60	(66)
10-(2-Cyanoethyl)-	158-159	(145)
10-Decyl-	183-185/0.5 mm.*	(66)
10-Ethyl-	101-103	(11, 14, 68)
	103-104.5	(63)
10-Isopropyl-	59-60	(63)
10-(*p*-Methoxybenzyl)-	101.5-103	(63)
10-Methyl-	99	(14)
	101-103	(11, 64)
10-Octadecyl-	53	(66)
10-Propyl-	49-50	(63)

* Boiling point.

TABLE 4

10-Acyl, 10-aroyl, and 10-sulfonyl derivatives of phenothiazine

Substituents	Melting Point	References
	°C.	
10-(*p*-Acetamidobenzenesulfonyl)-	204-206	(11)
10-Acetyl-	197-198	(14)
10-(*N*-Acetylsulfanilyl)-	209	(90)
10-Benzenesulfonyl-	170-170.5	(82)
10-Benzoyl-	170.5	(59)
10-Carboethoxy-	109-110	(59)
10-(*o*-Carboxybenzoyl)-	179-181	(165)
10-Chloroacetyl-	113.5-114.5	(41, 64)
10-(β-Chloropropionyl)-	142-143	(41)
10-Chlorocarboxy-	167.5	(59)
10-(α,β-Dibromopropionyl)-	135-135.5	(41)
10-Dichloroacetyl-	149-151	(64)
10-(*p*-Nitrobenzenesulfonyl)-	175-176	(11)
10-Phenylacetyl-	152-153	(64)
10-Succinyl-	181-182 (dec.)	(4)
10-Sulfanilyl-	182-184	(11)
10-(*p*-Toluenesulfonyl)-	155-156	(11)

TABLE 5

10-Aryl derivatives of phenothiazine

Substituents	Melting Point	References
	°C.	
10-(2'-Amino)phenyl-	139-139.5	(66)
10-(2'-Amino-4'-chloro)phenyl-	125-126	(66)
10-(2'-Amino-4'-methoxy)phenyl-	180-181	(66)
10-(2'-Amino-4'-methyl)phenyl-	140-140.5	(66)
10-(4'-Amino)phenyl-	132-133	(66)
10-(2'-Carbomethoxy)phenyl-	143-144	(67)
10-(3'-Carbomethoxy)phenyl-	98-99	(68)
10-(4'-Carbomethoxy)phenyl-	140.5-141.5	(68)
10-(2'-Carboxy)phenyl-	214-215	(67)
10-(3'-Carboxy)phenyl-	254-255	(68)
10-(4'-Carboxy)phenyl-	221-221.5	(68)
10-(2'-Methyl)phenyl-	101-101.5	(65)
10-(4'-Methyl)phenyl-	135-136	(65)
10-(2'-Nitro)phenyl-	156-157	(66)
10-(4'-Nitro)phenyl-	157	(66)
10-(2'-Nitro-4'-chloro)phenyl-	185-186.5	(66)
10-(2'-Nitro-4'-methoxy)phenyl-	184-186	(66)
10-(2'-Nitro-4'-methyl)phenyl-	179.5-180	(66)
10-Phenyl-	89-90	(6, 57)
	94.5	(68)

TABLE 6

Nuclear-substituted and 10-substituted phenothiazines

Substituents	Melting Point	References
	°C.	
10-Acetyl-2-acetyl-	105–106	(4)
10-Acetyl-2,8-diacetamido-	302	(115)
10-Acetyl-2,8-diacetyl-	199-202	(115)
10-Acetyl-3-methoxy-	121–121.5	(66)
10-Acetyl-3-nitro-	146	(64)
10-Benzenesulfonyl-3,7-dinitro-	300 (dec.)	(82)
10-Benzoyl-1,3-dinitro-	209	(95)
10-Carboxyethyl-2-trifluoromethyl-	159.5–160	(146)
10-Ethyl-3-acetoxymercuri-	151–153	(57, 68)
10-Ethyl-3-bromo-	121–122	(63)
10-Ethyl-2-carboethoxy-	62.5–63.5	(4)
10-Ethyl-2-carbomethoxy-	84.5–85.5	(4)
10-Ethyl-2-carboxy-	184–185	(4)
10-Ethyl-3-carboxy-	197.5–198.5	(68)
10-Ethyl-4-carboxy-	178–179	(68)
10-Ethyl-3-chloro-	111–113	(63)
10-Ethyl-3,7-diacetoxymercuri-	300 (dec.)	(57)
10-Ethyl-3-iodo-	126–127	(68)
10-Ethyl-4-iodo-	118–119	(63)
10-Formyl-1,3-dinitro-	243	(155)
10-Methyl-3-acetamido-	169	(99)
10-Methyl-3-acetoxymercuri-	165	(57)
10-Methyl-3-amino-		(99)
10-Methyl-3-chloro-	107	(126)
10-Methyl-3-chloro-x,x-dinitro-	215	(126)
10-Methyl-3,7-diacetamido-	265	(99)
10-Methyl-3,7-diacetoxymercuri-	300 (dec.)	(57)
10-Methyl-3,7-diamino-		(99)
10-Methyl-3,7-dibromo-	198	(57)
10-Methyl-3-formyl-	89	(25)
10-Methyl-3-iodo-	107	(57)
10-Methyl-3-methyl-	148	(25)
10-Methyl-3-nitro-	177	(99)
10-Methyl-3,7-dinitro	280 (dec.)	(99)
10-Methyl-3-styryl-	152	(25)
10-Phenyl-1-carbomethoxy-	123–124.5	(67)
10-Phenyl-4-carbomethoxy-	133–134	(68)
10-Phenyl-4-carboxy-	258–258.5	(68)

TABLE 7

Sulfoxides (5-oxides) of derivatives of phenothiazine

Substituents	Melting Point	References
	°C.	
10-Acetyl-	169.5–170	(64)
10-Acetyl-3-nitro-	156–159	(64)
10-Acetyl-3,7-dinitro-	265–267	(66)
10-Benzoyl-1,3-dinitro-	209	(95)
10-Benzoyl-3-nitro-	360 (dec.)	(82)
10-Benzyl-	226.5–228	(63)
10-Chloroacetyl-	186–187	(64)
10-(β-Chloroethyl)-	154–155	(66)
10-Decyl-3-nitro-	102.5–103	(66)
3,7-Dimethyl-	259	(93)
3,7-Dinitro-		(34)
10-Ethyl-	162–164	(63)
10-Ethyl-4-carbomethoxy-	168–169	(63)

TABLE 7—*Concluded*

Substituents	Melting Point	References
	°C.	
10-Ethyl-4-carboxy-	226 (dec.)	(63)
10-Ethyl-4-carboxylic acid hydrazide	225–226	(63)
10-Ethyl-3-chloro-	112–114	(63)
10-Ethyl-3-nitro	204.5–205	(66)
3-Methoxy-	198	(93)
10-(*p*-Methoxybenzyl)-	202.5–204	(63)
10-Methyl-	193	(6)
10-Methyl-3,7-diacetamido	270 (dec.)	(99)
10-Methyl-3-nitro-		(99)
10-Octadecyl-	98	(66)
3-Octyloxy-	168.2–168.7	(88)
10-Phenyl-	170–171	(66)
10-Phenyl-3-nitro-	223.5–224.5	(66)
10-Phenylacetyl-	141–141.5	(64)

TABLE 8

Sulfones (5-dioxides) of derivatives of phenothiazine

Substituents	Melting Point	References
	°C.	
Phenothiazine 5-dioxide	257–258	(11, 147)
10-Acetyl-	216–217	(64)
10-Benzyl-	211–212	(45)
	284–286	(63)
10-Carboethoxy-	215–216	(11)
10-(2-Carboxyethyl)-	189.5–190	(146)
10-Chloroacetyl-	211	(64)
10-(2-Cyanoethyl)-	233–234	(146)
2,8-Diacetyl-	309–312 (dec.)	(115)
2,8-Diamino-	355–356	(115)
2,8-Dicarboxy-	Above 360 (dec.)	(115)
2,8-Dicarboxylic acid azide	365–375 (dec.)	(115)
2,8-Dicarboxylic acid chloride	Above 360 (dec.)	(115)
10-Dichloroacetyl-	211–212	(64)
2,8-Diisocyanate	335–340	(115)
3,7-Dinitro-	320	(34)
10-Ethyl-	162–163	(11, 64)
10-Ethyl-3-amino-	186–187	(63)
10-Ethyl-3-carbomethoxy-	140–141	(63)
10-Ethyl-4-carboxy-	228–229	(63)
10-Ethyl-3-chloro-	154–156	(63)
10-Ethyl-3-chloroacetamido-	184.5–186	(63)
10-Ethyl-4-iodo-	194–195	(63)
10-Ethyl-3-nitro-	245–246.5	(63)
10-Isopropyl-	174–176	(63)
10-Methyl-	220–221 (dec.)	(64)
10-Phenyl-	204–205	(57)
10-Propyl-	193–195	(63)
10-Phenylacetyl-	215–216	(64)
10-(*p*-Toluenesulfonyl)-	246–248	(11)