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SYNTHESIS OF PHENOTHIAZINE DERIVATIVES FOR ANTIOXIDANT STUDIES

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ABSTRACT

As part of an investigation of the inhibitive properties of phenothiazine and its derivatives, and of the mechanism of their antioxidant action, the syntheses and characterization of a number of phenothiazine derivatives and their secondary amine precursors are described. Condensation of arylamines with aryl halides or phenols provided the desired aromatic secondary amines. The new amine compounds synthesized are 3-trifluoromethylphenyl-β-naphthylamine, 3-trifluoromethyldiphenylamine, and 3-trifluoromethyl-3′-methyldiphenylamine.

The thiazines were obtained from the corresponding asymmetrical and substituted diphenylamines by the iodine-catalyzed modification of Bernthsen's fusion with sulfur; the new preparations are 2-trifluoromethylphenothiazine, 2-trifluoromethyl-8-methylphenothiazine, and 3-isopropoxyphenothiazine.

Some of these thiazines reacted with acrylonitrile to give β-substituted propionitriles which were hydrolyzed to the corresponding acids. The new compounds are β-10-phenothiazylpropionitrile and β-(7-benzo[c]phenothiazyl)-propionitrile. A new method was used to prepare β-10-phenothiazylpropionic acid.

All the known oxidation products of phenothiazine were prepared by previously described procedures.

The investigation was extended to include acridine, phenazine, and carbazole derivatives. The new carbazole structures are β-(3,6-di-tert-butyl-9-carbazyl)-propionitrile, β-(3,6-di-tert-butyl-9-carbazyl)-propionic acid, β-(1,2,3,4-tetrahydro-9-carbazyl)-propionitrile and β-(1,2,3,4-tetrahydro-9-carbazyl)-propionic acid.

PROBLEM STATUS

This is an interim report on the problem; work is continuing.

AUTHORIZATION

NRL Problem C02-06D (BuAer Problem TED 0405)
NA 350-064

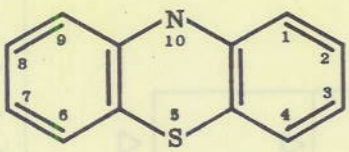
SYNTHESIS OF PHENOTHIAZINE DERIVATIVES FOR ANTIOXIDANT STUDIES

INTRODUCTION

Several investigators have reported the use of phenothiazine as an effective antioxidant for synthetic lubricants (1,2,3). However, early work at this Laboratory indicated that its usefulness as a lubricant additive was limited by excessive volatility at elevated temperatures. Accordingly, a project was initiated to synthesize phenothiazine derivatives and analogs of interest, to test them as antioxidants, and to study their mode of action. The organic synthetic phase of that investigation is presented here; the results of the study of the antioxidant properties of these compounds and a theoretical discussion of the findings are given elsewhere (4).

CHARACTERIZATION OF PHENOTHIAZINE

The phenothiazine molecule is made up of two benzene rings fused at the ortho positions to a thiazine nucleus in a linear arrangement. In the pure state it is a yellow crystalline substance melting at 185°. Phenothiazine is the preferred name for this heterocyclic compound; other accepted names are phenthiazine, thiodiphenylamine, and dibenzo-1,4-thiazine. The two numbering systems most often encountered in the literature are illustrated below:*



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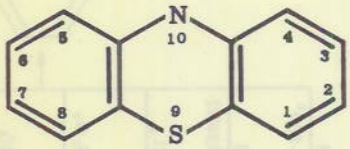

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Several methods available for the preparation of phenothiazine are shown in Figure 1, the most common being the fusion of diphenylamine with sulfur in the presence of a trace of iodine.

Presented for general interest, Figure 2 illustrates some reactions of phenothiazine resulting in ring rupture and dethionation.

** The naming and numbering of compounds reported in this investigation are the same as used in Chemical Abstracts indexes.*

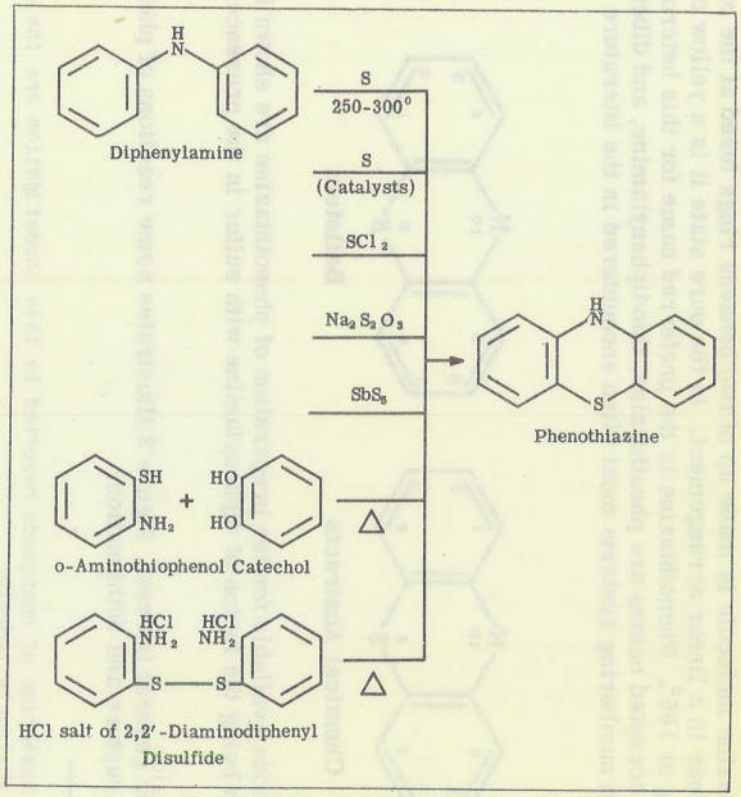

Figure 1 - Some methods of preparation of phenothiazine

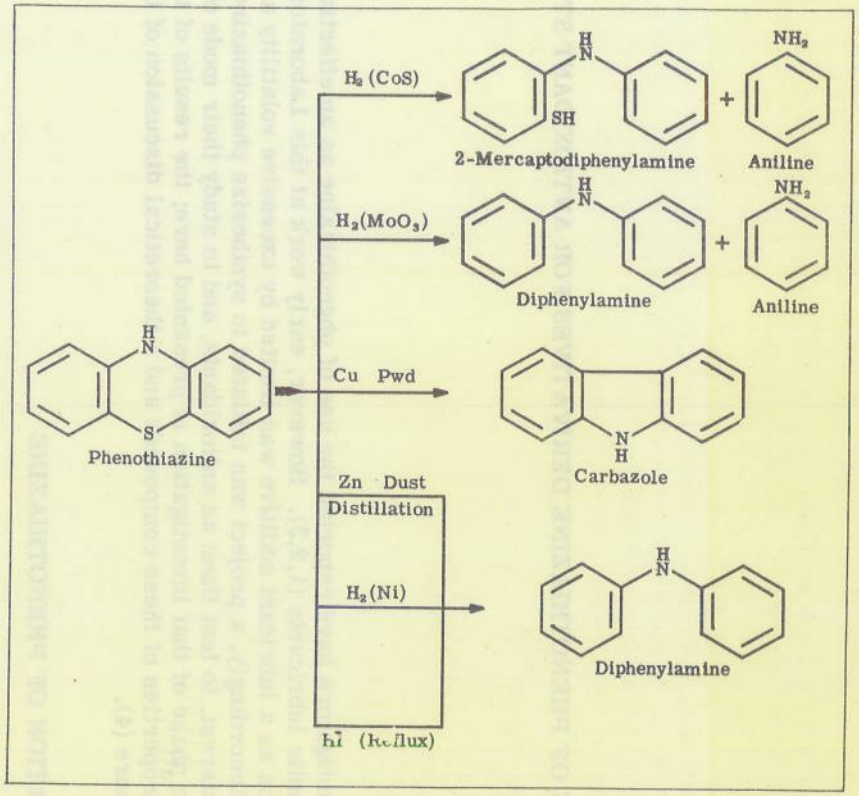

Figure 2 - Reactions of phenothiazine resulting in ring rupture and dethionation

SYNTHESIS OF PHENOTHIAZINE DERIVATIVES AND ANALOGS

Heterocyclic compounds with alkyl, aryl, and halogen substituents on both the ring and hetero atoms were prepared to increase the molecular weight, to effect changes in the physical constants and chemical properties, and to produce variations in the condition of molecular resonants. Some of the compounds obtained were expected to have less volatility and others more effective antioxidant action than the parent compound. Still others were prepared to assist in elucidating the mechanism of the antioxidant group.

For the purpose of this work, phenothiazine derivatives and analogs of probable interest as antioxidants are classified into four groups:

1) Carbocyclic ring-substituted phenothiazines,
2) Nitrogen-substituted phenothiazines,
3) Oxidation products of phenothiazine,
4) Other nitrogen-containing heterocyclic compounds.

Carbocyclic Ring-Substituted Phenothiazines

The ring-substituted phenothiazines were most advantageously prepared by the thionation of the corresponding aromatic secondary amines. For the preparation of the diarylamines, consideration was given to the ease of synthesis from readily available materials. The commercial rubber antioxidants served as a convenient source of many amines used in this investigation. The remainder of the amine precursors were synthesized by the method of Goldberg (5) or the more recent method described by Buu-Hoi (6).* In the former procedure, the aromatic secondary amine was prepared by the copper-catalyzed reaction of a primary amine and an aryl halide, usually in nitrobenzene solution. For the preparation of polyaromatic secondary amines, the more convenient method of Buu-Hoi, employing aromatic hydroxy compounds and aromatic amines in the presence of iodine, was used. An iodine-catalyzed modification of Bernthsen's fusion (7) of these diarylamines with sulfur provided the carbocyclic ring-substituted phenothiazines required for the antioxidant investigation.

The combination of the methods of Goldberg and Bernthsen was used to prepare most of the ring-substituted phenothiazines reported. The procedure is illustrated in Figure 3, which specifically outlines the method of preparation of 2-trifluoromethylphenothiazine.

The position of substitution for the thionation products of meta-substituted diphenylamines has received the attention of a number of investigators. It is shown in Figure 3 that the trifluoromethyl group may be substituted in either the 2- or the 4-position of phenothiazine. Baltzly (9) obtained substitution in either the 2- or 4-position for the haloform reaction product of acetylphenothiazine. This structure differed from the phenothiazinecarboxylic acid reported by Gilman (10), which was obtained by metalation and carbonation. However, both products afforded diphenylamine-3-carboxylic acid on dethionation. Calcott (11) reported 2- or 4-substituted methylene blues prepared by the action of an oxidizing agent on para-amino-dimethylaniline, ortho-substituted dimethylaniline, and sodium thiosulfate. Since the position of the trifluoromethyl group on the phenothiazine nucleus is of considerable interest in inhibitor studies, it was decided to submit the

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* *See also reference 8 for the Ullman method of synthesis.*

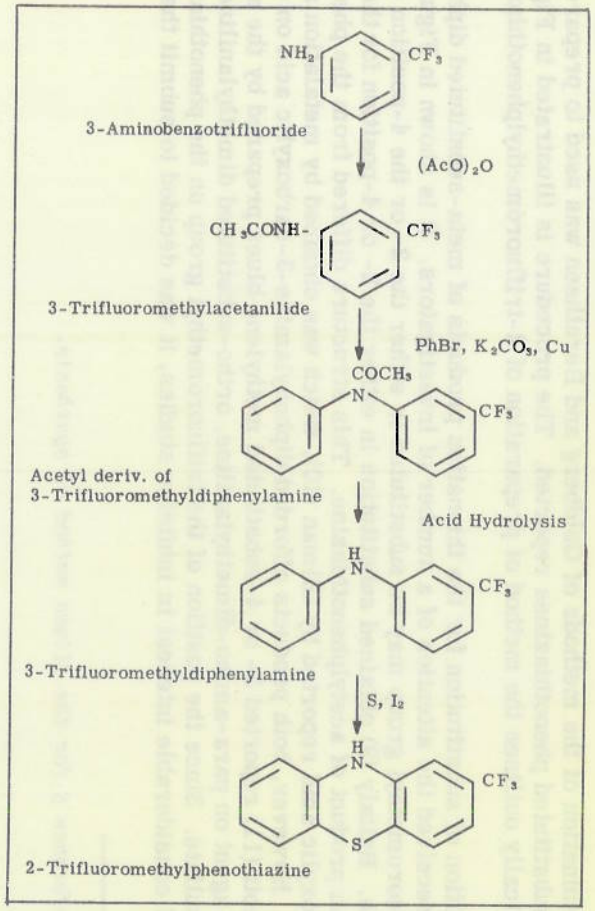

Figure 3 - Synthesis of 2-trifluoromethylphenothiazine

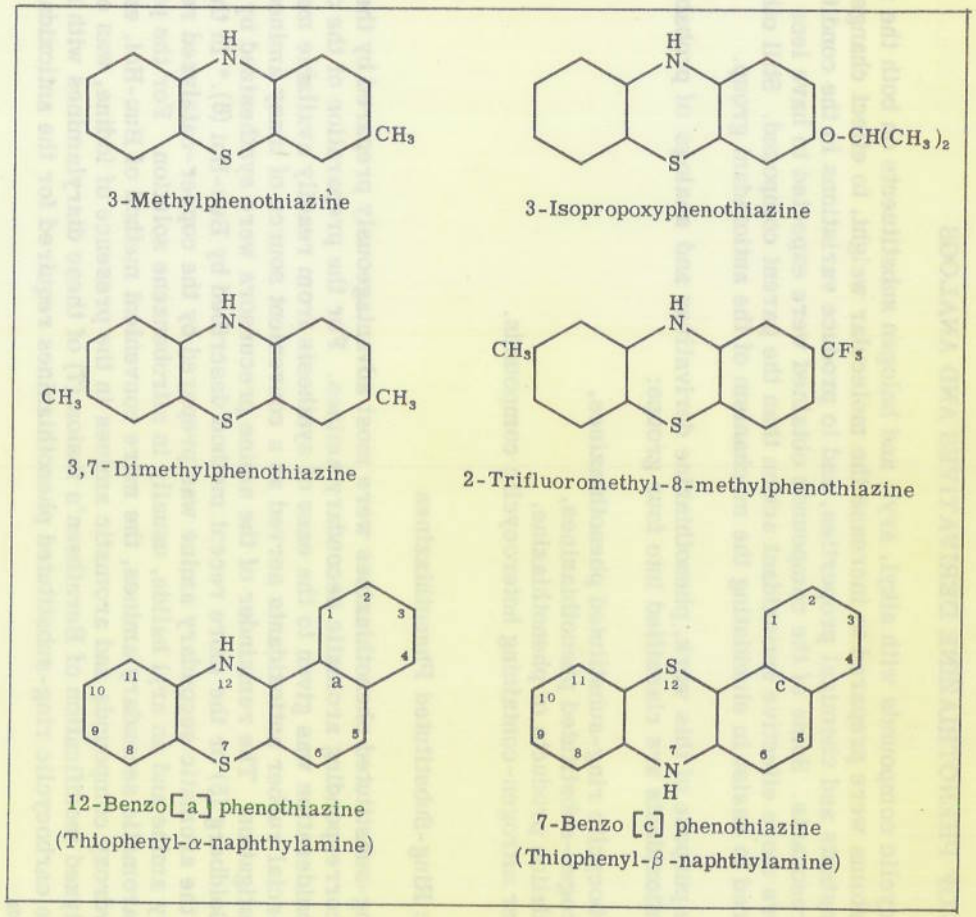

Figure 4 - Carbocyclic ring-substituted phenothiazines

compound to spectral examination. The results furnish evidence that the substitution takes place in the 2-position.*

The structures of other ring-substituted phenothiazines prepared in the investigation are shown in Figure 4.

The preparation of substituted phenothiazines by the Friedel-Crafts hydrocarbon and ketone synthesis (9) usually yielded reaction products difficult to isolate. Direct tert-butylation of phenothiazine proved unsuccessful using aluminum chloride, aluminum bromide, zinc chloride, or stannic chloride as catalysts.

The Friedel-Crafts reactions with phenothiazine discussed in the text are summarized in Figure 5, which includes the synthesis and degradation of the phenothiazinecarboxylic acids independently reported by Baltzly (9) and Gilman (10).

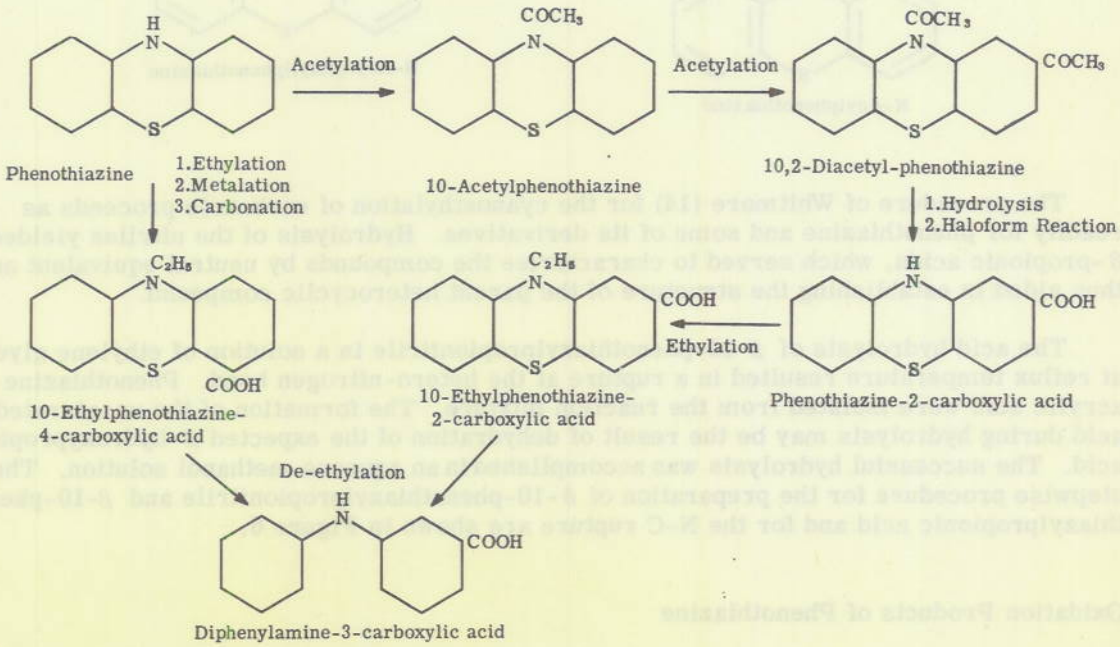

Figure 5 - Some Friedel-Crafts reactions with phenothiazine

Nitrogen-Substituted Phenothiazines

To determine the antioxidant effect of N-substitution, a number of aryl- and alkyl-phenothiazines were synthesized. The active NH group in the heterocyclic combination reacted to give a variety of alkyl (10, 12), aryl (10), and acyl (9) groups. For the preparation of the lower alkyl derivatives, the reaction of the alkyl halide with phenothiazine in a sealed tube was used. The aryl and higher alkyl derivatives were synthesized from the appropriate halide and phenothiazine in the presence of potassium carbonate and copper

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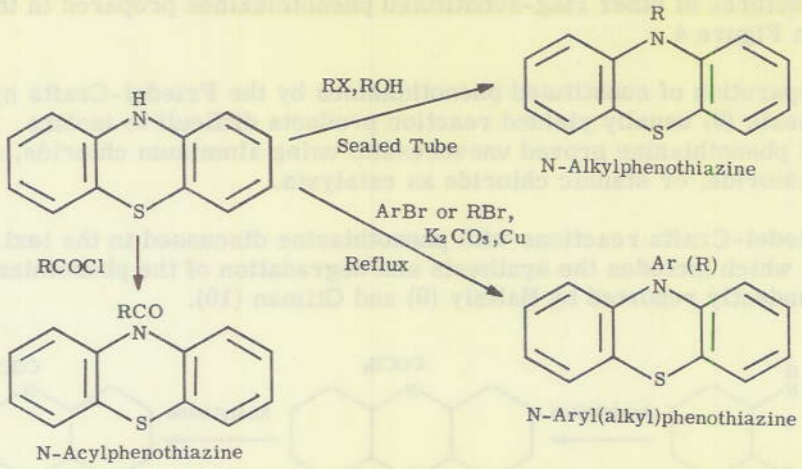
* *The infrared studies were made by Dr. D. C. Smith of this Laboratory. See Appendix II for detailed report.*

powder (or copper bronze). The acyl derivatives were obtained by heating the acid chloride and phenothiazine in the absence of a solvent (13). These reactions are illustrated below.



The procedure of Whitmore (14) for the cyanoethylation of carbazole proceeds as readily for phenothiazine and some of its derivatives. Hydrolysis of the nitriles yielded β-propionic acids, which served to characterize the compounds by neutral equivalent and thus aided in establishing the structure of the parent heterocyclic compound.

The acid hydrolysis of β-10-phenothiazylpropionitrile in a solution of ethylene glycol at reflux temperature resulted in a rupture at the hetero-nitrogen bond. Phenothiazine and acrylic acid were isolated from the reaction mixture. The formation of the unsaturated acid during hydrolysis may be the result of dehydration of the expected β-hydroxypropionic acid. The successful hydrolysis was accomplished in an aqueous methanol solution. The stepwise procedure for the preparation of β-10-phenothiazylpropionitrile and β-10-phenothiazylpropionic acid and for the N-C rupture are shown in Figure 6.

Oxidation Products of Phenothiazine

The oxidation products of phenothiazine are of interest for the evaluation of the inhibitor action of the parent compound. To determine the role of sulfur and nitrogen in the process, oxidation products involving these hetero atoms were prepared. The action of hydrogen peroxide on phenothiazine in the presence of alcoholic potassium hydroxide (15) provided phenothiazine-5-oxide (diphenylamine sulfoxide). Phenothiazine-5-dioxide (diphenylamine sulfone) was prepared by heating 10-methylphenothiazine-5-dioxide with hydriodic acid. The sulfone was synthesized by the oxidation of 10-methylphenothiazine with calcium permanganate (16). Phenothiazine yielded diphenothiazine (o-dithiotetraphenylhydrazine) when heated with yellow oxide of mercury (17). Figure 7 shows the oxidation reactions involving the hetero atoms of phenothiazine.

Oxidation reactions were extended to the benzene nucleus to provide phenothiazone-3 and 7-hydroxyphenothiazone-3 (thionol). The former was prepared by the action of ferric chloride on phenothiazine (18); the latter requires the action of hydrogen peroxide on phenothiazine in the presence of alcoholic hydrochloric acid (18,19).

The ring oxidation reactions of phenothiazine and the methods of preparation for the alkyl ethers are shown in Figure 8, together with the equilibrium reactions of the thiazones, the respective leuco bases, and the formation of alkyl ethers (20).

Other Nitrogen-Containing Heterocyclic Compounds

For comparative purposes, the investigation was extended to include the synthesis of phenazine, carbazole, phenoselenazine, and acridine derivatives. The procedures reported by Clemo and McIlwain (21) were used to prepare phenazine, dihydrophenazine, tetrahydrophenazine, and phenazhydrin. Phenoselenazine was obtained by the reaction of diphenylamine and selenium dioxide (22). The preparation of hendecylacridine was conveniently carried out by the action of zinc chloride on lauric acid and diphenylamine (23). The structure of some of the heterocyclic compounds discussed here are shown in Figure 9.

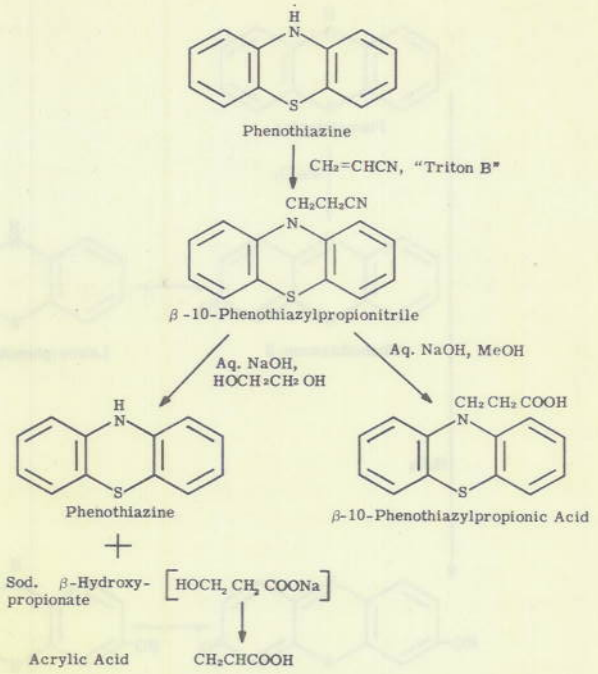


Figure 6 - Cyanoethylation of phenothiazine

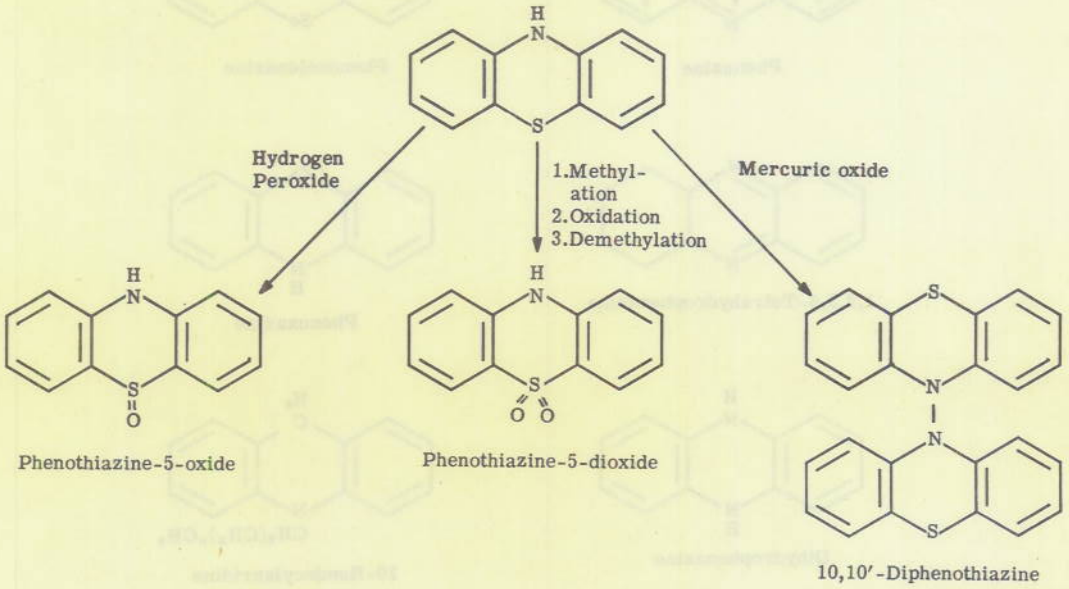


Figure 7 - Oxidation products involving the hetero atoms of phenothiazine

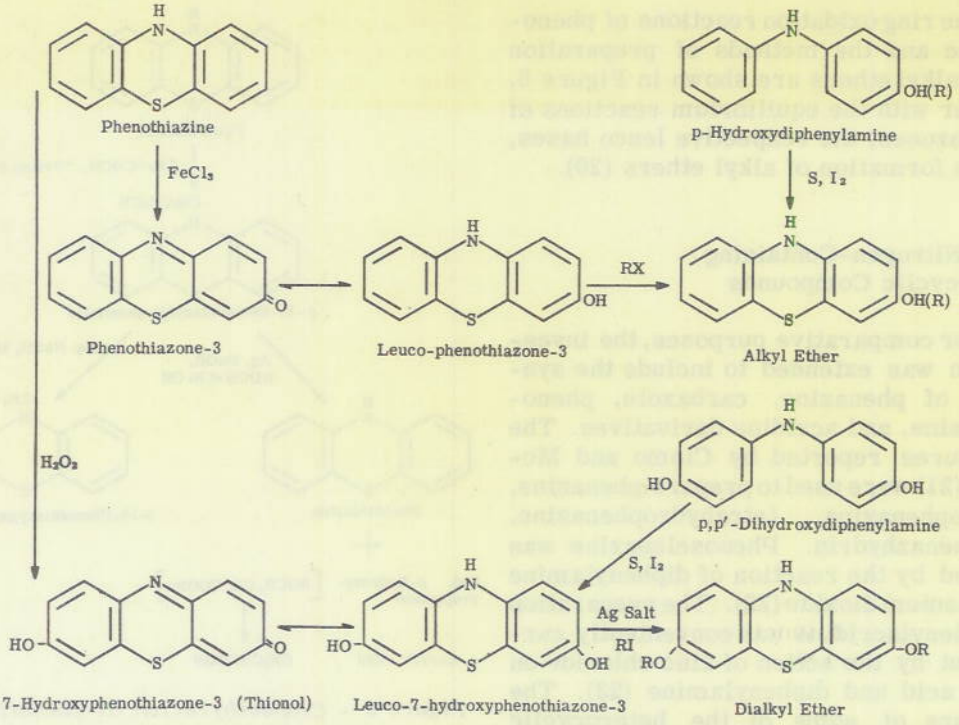


Figure 8 - Ring oxidation products of phenothiazine and their alkyl ethers

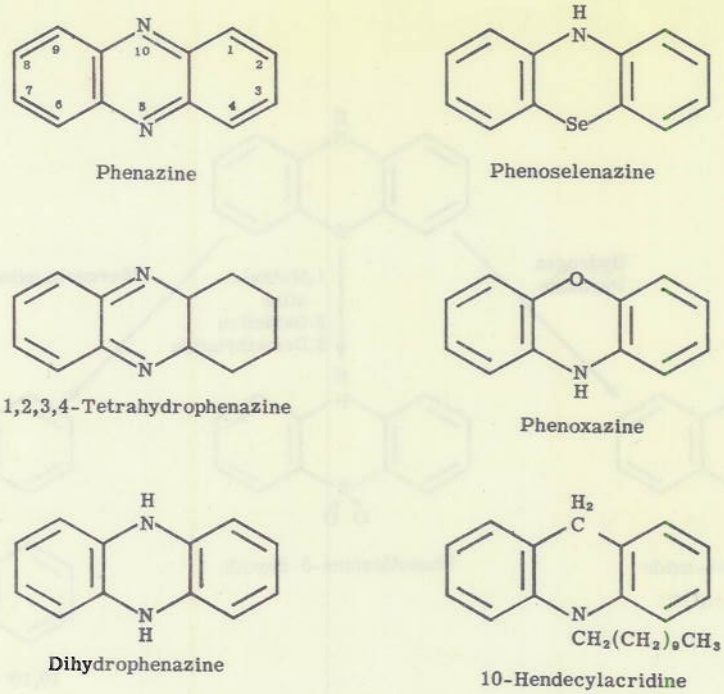


Figure 9 - Some analogs of phenothiazine

Carbazole, tetrahydrocarbazole, and di-tert-butylcarbazole were subjected to cyanoethylation and the reaction products hydrolyzed to the corresponding acids. The reaction steps for the preparation of β-(1,2,3,4-tetrahydro-9-carbazyl)-propionitrile and β-(1,2,3,4-tetrahydro-9-carbazyl)-propionic acid are shown in Figure 10.

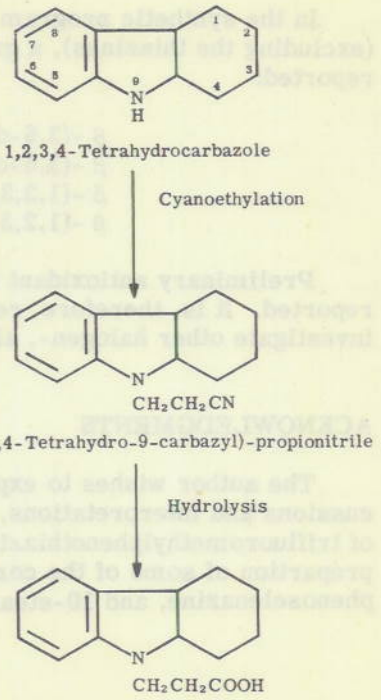


Figure 10 - Synthesis of β-(1,2,3,4-tetrahydro-9-carbazyl)-propionic acid

The methods used for the preparation of the phenothiazine derivatives and analogs are described in detail in Appendix I. The order of presentation follows the discussion in the text.

SUMMARY AND RECOMMENDATIONS

The purpose of the work here reported was to synthesize a variety of phenothiazine derivatives and analogs with properties making them of interest as antioxidants. To explore the possible effects of increased molecular weight, position of substitution, and variations in functional group on inhibition, a synthetic program was carried out to provide aryl, alkyl, acyl, and halogen adducts of phenothiazine. Compounds with mono-, di-, and tri-substitutions involving the 2, 3, 4, 5, 6, 7, 8, or 10 positions in the phenothiazine nucleus were made available. These substituents were varied to include methyl, ethyl, tert-butyl, hendecyl, octadecyl, phenyl, benzyl, benzoyl, benzo, trifluoromethyl, methoxy, and isopropoxy groups. The total number of phenothiazine derivatives and amine precursors described is twenty-seven; the following eight are new:

3-(trifluoromethyl) phenyl-β-naphthylamine
3-trifluoromethyldiphenylamine
3-trifluoromethyl-3′-methyldiphenylamine
2-trifluoromethylphenothiazine
2-trifluoromethyl-8-methylphenothiazine
3-isopropoxyphenothiazine
β-10-phenothiazylpropionitrile
β-(7-benzo[c]phenothiazyl)-propionitrile
β-10-phenothiazylpropionic acid (prepared by a new method)

Of particular interest in the study of phenothiazine as an antioxidant was the hetero atom and ring oxidation products; therefore all known compounds in this class were synthesized.

For comparative studies, a variety of nitrogen-containing heterocyclics were prepared. This group of compounds included linear three-ring heterocyclics with the center nucleus containing N-Se, N-O, N-N, N-C, and N, with or without substitutions.

Some of the thiazines reacted with acrylonitrile to give β-substituted propionitriles which were hydrolyzed to the corresponding acids. The acids served to characterize the structures by neutral equivalent.

In the synthetic program which describes fourteen nitrogen-containing heterocyclics (excluding the thiazines), a group of four new substituted carbazole derivatives are reported:

β -(3,6-di-tert-butyl-9-carbazyl)-propionitrile
β -(3,6-di-tert-butyl-9-carbazyl)-propionic acid
β -(1,2,3,4-tetrahydro-9-carbazyl)-propionitrile
β -(1,2,3,4-tetrahydro-9-carbazyl)-propionic acid.

Preliminary antioxidant tests indicate promising results for many of the compounds reported. It is, therefore, recommended that the synthetic program be continued to investigate other halogen-, alkyl-, and aryl-substituted thiazines.

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. W. A. Zisman for helpful discussions and interpretations, to Dr. D. C. Smith and L. W. Daasch for infrared analyses of trifluoromethylphenothiazine, and to Mrs. D. Workman for technical assistance in the prepartion of some of the compounds. Mr. F. L. Schmehl prepared 10-hendecylacridine, phenoselenazine, and 10-stearoylphenothiazine.

* * *

APPENDIX I
Preparation of Compounds*

3-Trifluoromethyldiphenylamine - 3-Aminobenzotrifluoride (product of Hooker Electrochemical Company) was first converted to the acetyl derivative with acetic anhydride. A mixture of 20.3 g (0.1 mole) of 3-trifluoroacetanilide (m.p. 103°) and 31.4 g (0.2 mole) of bromobenzene was stirred under reflux in 100 ml of nitrobenzene for 21 hours in the presence of 15 g of anhydrous potassium carbonate and 0.5 g of cuprous bromide, after which the nitrobenzene and unchanged bromobenzene were removed by steam. The crude N-acetyl-3-trifluoromethyldiphenylamine (b.p. 125-127°/0.5 mm), obtained in 72% (21.0 g) yield, was hydrolyzed by refluxing for four hours with 30 ml of ethanol and 30 ml of concentrated hydrochloric acid. The product was poured onto ice, and the precipitate extracted with ether, dried over sodium sulfate, the solvent removed, and the residue distilled. 3-Trifluoromethyldiphenylamine (10.6 g, 56% yield) distilled as a yellow liquid (b.p. 108-110°/0.3mm, n_D^{25} 1.5655). It yielded a picrate from benzene (coarse yellow needles, m.p. 147°). The amine is steam distillable.

Anal. Calc'd. for $C_{13}H_{10}NF_3$: N, 5.90. Found: N, 5.90. †

2-Trifluoromethylphenothiazine - To 7.0 g (0.03 mole) of 3-trifluoromethyldiphenylamine was added 2.3 g of sublimed sulfur and 0.2 g of iodine. The mixture was heated at 140-150° for one hour. The reaction product was cooled, dissolved in toluene, treated with filter-cel and charcoal, filtered, and the solution allowed to crystallize. The crude 2-trifluoromethylphenothiazine (3.5 g, 44% yield) was recrystallized from alcohol as yellow platelets, m.p. 188-189°. The compound imparts to concentrated sulfuric acid a brown color which remains unchanged on dilution with water or the addition of nitric acid.

Anal. Calc'd. for $C_{13}H_8NSF_3$: C, 58.20; H, 3.16. Found: C, 57.56; H, 3.22.

3-Trifluoromethyl-3 -methyldiphenylamine - A mixture of 50.3 g (0.25 mole) of m-trifluoromethylacetanilide, 85.5 g (0.5 mole) of m-bromotoluene, 33.0 g. of anhydrous potassium carbonate, 1.0 g of cuprous bromide, and 300 ml of dry nitrobenzene were heated under reflux for 18 hours. The nitrobenzene was steam-distilled, and the residue was refluxed for one hour with 75 ml of concentrated hydrochloric acid and 75 ml of ethanol. The solvent was removed and the reaction product washed thoroughly with water. The amine distilled as a yellow oil (24 g, 39%) b.p. 130-132°/1 mm, n_D^{25} 1.5581. The hydrochloride melted at 228° with decomposition.

Anal Calc'd. for $C_{14}H_{12}NF_3$: N, 5.58. Found: N, 5.92.

2-Trifluoromethyl-8-methylphenothiazine - Two grams of 3-trifluoromethyl-3'-methyldiphenylamine, 0.5 g of sulfur, and a small crystal of iodine were heated in an oil-bath maintained at 145-150° for one hour. The reaction product was cooled, dissolved in benzene, treated with decolorizing charcoal and filter-cel, filtered, and allowed to crystallize.

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* *All melting points are uncorrected.*

† *The microanalyses were performed by Oakwold Laboratories, Alexandria, Va.*

The product was recrystallized from benzene as yellow platelets (m.p. 227-228°) in 52% yield (1.3 g).

Anal. Calc'd. for $C_{14}H_{10}NSF_3$: N, 4.98. Found: N, 4.98

4-Methyldiphenylamine - The condensation product of acetanilide and p-bromotoluene conducted in presence of copper bronze gave a product melting at 88° (5).*

Di-p-tolylamine - This compound is the hydrolysis product of the condensation of p-acetyltoluidine and p-bromotoluene in the presence of copper bronze, m.p. 81°(24).

3,7-Dimethylphenothiazine - The thionation of p,p'-ditolylamine (1.0 g) was carried out at 175° for 1 hour in the presence of iodine as catalyst. The product (0.78 g) crystallized from acetic acid in greenish-yellow leaflets, m.p. 220°. The procedure described by Kehrmann (24) requires a longer reaction period and a temperature of 220°.

3-Isopropoxyphenothiazine - The reaction of sulfur and p-isopropoxydiphenylamine at 130-140° for one-half hour in the presence of iodine as catalyst yielded yellow crystals from light petroleum ether, m.p. 123-124° (20).

Anal. Calc'd. for $C_{15}H_{15}ONS$: C, 70.05; H, 5.88. Found: C, 70.37; H, 6.06.

7-Benzo[c]phenothiazine (Thiophenyl-β-naphthylamine) - Iodine-catalyzed fusion of phenyl-β-naphthylamine and sulfur at 160-170° for one hour afforded yellow crystals from alcohol, m.p. 178°. The uncatalyzed reaction requires six hours at a temperature of 210° (25,26).

12-Benzo[a]phenothiazine (Thiophenyl-α-naphthylamine) - Iodine-catalyzed reaction of phenyl-α-naphthylamine and sulfur yielded yellow crystals, m.p. 138° (25,26).

3-(Trifluoromethyl)phenyl-β-naphthylamine - A mixture of 72.0 g (0.5 mole) of β-naphthol and 80.5 g (0.5 mole) of m-trifluoromethylaniline was heated under reflux for 24 hours in the presence of 0.5 g of iodine. The resulting dark oil was taken up in toluene, washed with aqueous sodium hydroxide, and dried over sodium sulfate. After removal of the solvent the residue was distilled in vacuo, b.p. 180-185°/2 mm. The reddish-brown distillate (71 g) solidified on cooling. Recrystallization from alcohol yielded white needles, m.p. 83-84°.

Anal. Calc'd. for $C_{17}H_{12}NF_3$: N, 4.87. Found: N, 5.22.

β-10-Phenothiazylpropionitrile - A mixture of 200 g (1 mole) of phenothiazine† and 300 ml of acrylonitrile was cooled in an ice-bath and treated with 3 ml of 40% aqueous solution of benzyltrimethylammonium hydroxide. A sudden reaction took place with considerable evolution of heat. The reaction product was warmed on a steam bath for an hour and then allowed to cool. The crystalline mass was filtered and vacuum-dried; yield 235 g (93%) of crude product. Two recrystallizations from acetone gave 171 g (73% recovery) of thick, colorless needles, m.p. 157°. No solid picrate is formed. The nitrile was soluble in hot benzene and acetone; less soluble in methanol and ethanol.

Anal. Calc'd. for $C_{15}H_{12}N_2S$: N, 11.16; S, 12.73. Found: N, 11.20; S, 12.77.

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* *In this case, and in every other case hereafter, whenever a reference and a melting point are cited together the value given agrees within one degree of that reported in the reference.*

† *N. F. purified; manufactured by Dow Chemical Company.*

β-10-Phenothiazylpropionic acid - The successful hydrolysis of the nitrile was accomplished by boiling a mixture of 25 g of β-10-phenothiazylpropionitrile, 25 g of sodium hydroxide, 75 ml of water, and 250 ml of methanol under reflux for 15 hours. The hydrolysis product was poured into ice-water, acidified with dilute hydrochloric acid, filtered, and crystallized from ethanol. The acid (17.5 g) was recovered in the form of fine, white needles, m.p. 164°*; neutral equivalent, 272 (calc'd., 271.4).

An attempt to prepare the acid in ethylene glycol failed. A mixture of 25 g (0.10 mole) β-10-phenothiazylpropionitrile, 250 ml of ethylene glycol, 25 g of sodium hydroxide, and 40 ml of water was boiled under reflux for 6.5 hours. The hydrolysis product was cooled, filtered, and the solid mass crystallized from alcohol, m.p. 185°. Mixed m.p. with an authentic sample of phenothiazine showed no depression. The other cleavage product, found in the filtrate, was identified as acrylic acid, b.p. 141°, and characterized by the methyl ester, b.p. 80°.

The anhydride of β-10-phenothiazylpropionic acid was obtained by warming the acid in xylene until the anhydride precipitated from solution. Recrystallization from alcohol afforded a granular product, m.p. 228° (decomp.). The original acid was recovered from aqueous alkali solution.

β-(7-Benzo[c]phenothiazyl)-propionitrile - A mixture of acrylonitrile and 7-benzo-[c]phenothiazine were made to react by the addition of "Triton B."† The reaction product (57% yield) was isolated as yellow crystals from acetic acid, m.p. 215°.

10-Stearoylphenothiazine - This compound was prepared by heating the acid chloride with phenothiazine without a solvent, m.p. 86° (13).

10-Benzoylphenothiazine - This compound was prepared by the reaction of benzoyl chloride with phenothiazine. It crystallized as leaflets from alcohol, m.p. 170-171° (28).

10-Acetylphenothiazine - This thiazine was readily obtained by boiling acetic anhydride and phenothiazine; white prisms, m.p. 197-198° (9).

2,10-Diacetylphenothiazine - The Friedel-Crafts reaction of acetyl chloride with 10-acetylphenothiazine yielded colorless needles, m.p. 105° (9).

2-Acetylphenothiazine - This compound was prepared by the acid hydrolysis of 2,10-diacetylphenothiazine, yellow needles, m.p. 192-193° (9).

10-Ethylphenothiazine - The compound was prepared by the reactions of ethyl iodide and phenothiazine in a steel bomb, white needles, m.p. 101-103° (10).

10-Octadecylphenothiazine - The compound was obtained by heating octadecyl bromide and phenothiazine in the presence of sodium carbonate, white needles, m.p. 53° (10).

10-Phenylphenothiazine - The compound was prepared by the reaction of iodobenzene and phenothiazine in the presence of potassium carbonate and copper powder, white prisms, m.p. 94° (10).

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* *Cauquil and Cassodevall (27) reported a m.p. of 161° for the acid prepared by the hydrolysis of the condensation product of ethyl β-bromopropionate and phenothiazine.*

† *Benzyltrimethylammonium hydroxide, 40% solution, product of Rohm and Haas, Philadelphia.*

10, 10'-Diphenothiazine (o-Dithiotetraphenylhydrazine) - The compound was prepared by the oxidation of phenothiazine with yellow mercuric oxide. The white amorphous powder is insoluble in ordinary solvents except benzene and chloroform. Decomposition begins about 245° without melting; no m.p. reported for this compound (17).

Phenothiazine-5-oxide (Diphenylamine sulfoxide) - This material was prepared by the oxidation of phenothiazine with hydrogen peroxide in the presence of alcoholic potassium hydroxide, white needles, m.p. 250° (15, 28).

Phenothiazine-5-dioxide (Diphenylamine sulfone) - Demethylation of 10-methylphenothiazine-5-dioxide yielded the desired product, m.p. 257° (29).

Phenothiazone-3 - The compound was prepared by the ferric chloride oxidation of phenothiazine in boiling alcohol, reddish-brown leaflets, m.p. 166° (18).

7-Hydroxyphenothiazone-3 (Thionol) - The compound was prepared by the method of De Eds and Eddy using hydrogen peroxide oxidation of phenothiazine in acid solution, deep reddish-brown crystals (15). The purity of the product is questionable (19).

1,2,3,4-Tetrahydrophenazine - o-Phenylenediamine and cyclohexane-1,2-dione* reacted in the presence of sodium acetate and acetic acid to give tetrahydrophenazine, yellow plates, m.p. 92° (21).

Phenazine - The iodine reduction of 1,2,3,4-tetrahydrophenazine in glacial acetic acid yielded yellow needles, m.p. 171° (21, 30).

Dihydrophenazine - The compound was prepared by the sodium hydrosulfite reduction of phenazine, white needles, m.p. 212° (31).

Phenazhydrin - This preparation is obtained by mixing equal amounts of phenazine and dihydrophenazine in hot petroleum ether, blue prisms, m.p. 209° (21).

Phenoselenazine - The compound was prepared by the action of selenium chloride on diphenylamine in benzene solution, yellow leaflets, m.p. 195° (22).

9-Hendecylacridine - The condensation of lauric acid with diphenylamine in the presence of zinc chloride at 200-230° gave the desired compound, m.p. 45° (23).

β-9-Carbazylpropionitrile - This material was prepared according to the directions of Whitmore et al. To a mixture of 167 g (1.0 mole) of carbazole† and 250 ml of acrylonitrile‡ cooled in an ice-bath was added 2.0 ml of "Triton B." A vigorous reaction ensued while the mixture was being stirred. The pasty mass was heated on a steam-bath for one hour and upon cooling the nitrile crystallized from solution. The product weighed 185 g (85%) and melted at 155° (14).

β-9-Carbazylpropionic acid - To 20 g (0.09 mole) of the nitrile was added 200 ml of 10% solution of sodium hydroxide. The mixture was boiled under reflux for 16.5 hours to

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* *Product of Hack Chemical and Oxygen Co., Ames, Iowa.*

† *Eastman Kodak Company, purest grade.*

‡ *Eastman Kodak Company, practical.*

complete hydrolysis. The sodium salt of the acid crystallized from solution on standing overnight. The filtered crystals were dissolved in water and neutralized with the calculated amount of hydrochloric acid. The white precipitate was filtered, washed twice with water, and crystallized from alcohol. The product of 19 g melted at 173° and gave a neutral equivalent of 138 (calc'd. 139) (32).

3,6-Di-tert-butylcarbazole - To a cold mixture of 185 g (2.0 moles) of tert-butyl chloride, 167 g (1.0 mole) of carbazole, and 100 ml of nitrobenzene was added 53.0 g (0.4 mole) of aluminum chloride over a fifteen-minute period while the mixture was stirred. A gentle reaction ensued when the mixture warmed to room temperature. The reaction product was allowed to stand overnight. The aluminum chloride complex was decomposed with 2N hydrochloric acid and ice. The organic layer was separated amd steam-distilled to remove the nitrobenzene. The product distilled at 171-175° under (0.3 mm) and weighed 215g (76%). The purified substituted carbazole melted at 228° and gave a picrate of fine, brick-red needles from alcohol, m.p. 209°C. Buu-Hoi and Cagniant (33) reported the compound but neglected to specify conditions for reaction.

β-(3,6-Di-tert-butyl-9-carbazyl)-propionitrile - A well-stirred mixture of 17.5 g (0.6 mole) of 3,6-di-tert-butylcarbazole and 20.0 g of acrylonitrile was cooled in an ice-bath and made to react by the addition of 0.5 ml of "Triton B." The reaction product was warmed on a steam-bath under a hood for one hour, and upon cooling a mass of crystals separated out. The nitrile was recrystallized from aqueous acetone yielding 12.0 g (59%) of fine white needles, m.p. 190.0-190.5°. Recrystallization from methanol did not raise the melting point. The product forms a picrate in alcohol which crystallized in reddish-brown needles, m.p. 184°.

Anal. Calc'd. for $C_{23}H_{28}N_2$: N, 8.75. Found: N, 8.98.

β-(3,6-Di-tert-butyl-9-carbazyl)-propionic acid - To 5 g (0.015 mole) of the nitrile in 50 ml of 90% ethanol was added 5 g of sodium hydroxide in 50 ml of 90% ethanol. The mixture was heated under reflux for 30 hours, after which only traces of ammonia could be detected. The solvent was removed from the reaction product and the free acid precipitated from the salt with hydrochloric acid. The product of 4.5 g (85%) crystallized from aqueous methanol in very fine, white needles, m.p. 193-194°. Mixed melting range of the acid and nitrile was 167-182°. The neutral equivalent was 355.0 (calc'd. 353.5). The substituted propionic acid is soluble in acetone, ethanol, methanol, benzene, and ethyl acetate. These oxygenated solvents are suitable crystallization solvents when diluted with water. The sodium salt of the acid is soluble in benzene; its aqueous solution foams freely.

The methyl ester, prepared by the E. Fischer method of esterification, crystallized as white platelets from acetone, m.p. 116.5-117.5°.

1,2,3,4-Tetrahydrocarbazole - The method of Rodgers and Carson was used to prepare a colorless product, m.p. 113-114° (34).

β-(1,2,3,4-Tetrahydro-9-carbazyl)-propionitrile - To a mixture of 41.0 g (0.24 mole) of 1,2,3,4-tetrahydrocarbazole and 60.0 g of acrylonitrile in an ice-bath was added 0.75 ml of "Triton B." The reaction product was warmed on a steam-bath for one hour and then cooled. The mass was recrystallized twice from acetone to yield 28.5 g (53%) of the nitrile; white needles, m.p. 115-116°.

Anal. Calc'd. for $C_{15}H_{16}N_2$: N, 12.45. Found: N, 12.26.

β-(1,2,3,4-Tetrahydro-9-carbazyl)-propionic acid - A mixture of 20.0 g of β-(1,2,3,4-tetrahydro-9-carbazyl)-propionitrile 100 ml of alcohol and 100 ml of 20% aqueous potassium hydroxide was boiled under reflux for 20 hours, cooled and acidified with hydrochloric acid. The tacky precipitate crystallized on stirring while cooling the flask under the tap. Recrystallization from alcohol yielded 18.0 g of white granular product, m.p. 118-119°; neutral equivalent, 242 (calc'd. 243.2).

Anal. Calc'd. for $C_{15}H_{17}O_2N$: N, 5.76. Found: N, 5.90.

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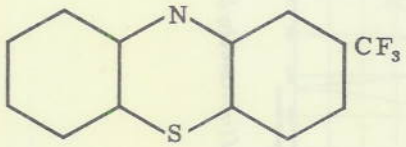
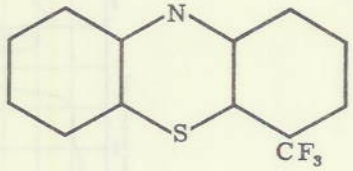
APPENDIX II
The Configuration of Trifluoromethylphenothiazine*

Since phenothiazine and its derivatives, as well as other heterocyclic compounds, do not undergo simple vibrational motions, it is unreasonable to expect to interpret the infrared spectra of these compounds in detail, to deduce detailed structural information. On the basis of presently available information, the only spectral evidence which would indicate whether the trifluoromethyl group is attached to the 2 position, as in Structure I, or to the 4 position, as in Structure II, is the following:



Structure I



Structure II

In Structure I there is one unsymmetrical trisubstituted ring, while in Structure II there is one vicinal trisubstituted ring. For benzene derivatives (not polycyclic compounds), the former structure produces a characteristic infrared band in the region 12.0 to 12.5 mu (35,36) while the latter produces a band in the region from about 12.5 to 13.15 mu (35,36). If these correlations are followed by these particular polycyclic compounds, then a strong infrared band in either of these regions would indicate, but not prove, the corresponding structure. The absence of any bands in either of these regions, however, would definitely rule out the corresponding structures, except for the possibility of violation of the correlation rules.

The spectra of phenothiazine and trifluoromethylphenothiazine were studied in the solid phase (using the petrolatum mull technique) over the range 2-22 mu (Figure 11). Trifluoromethylphenothiazine has a strong band at 12.17 mu which is not present in the phenothiazine spectrum and which falls within the 12.0-12.5 mu range characteristic of unsymmetrical trisubstituted rings, indicating that the CF_3 group is probably attached to the 2 position (Structure I). Also, there is no bond in either spectrum from 12.5 to 13.15 mu, indicating that there can be no vicinal trisubstituted rings (Structure II). Thus, the spectrum shows exactly the spectral features expected for Structure I.

It may be noted that both Structures I and II also have one ortho-disubstituted ring and that the parent molecule, phenothiozine, has two such rings. Since ortho-substituted benzenes have a characteristic band in the 13.15-13.5 mu region (35), a band would also be expected in this region for both compounds studied here. Trifluoromethylphenothiazine does have a strong band at 13.34 mu, while phenothiazine itself has two bands at 13.32 and 13.58 mu, the splitting in the latter case probably being caused by interactions between the two ortho-substituted rings. The fact that this correlation for ortho-disubstituted rings appears to be valid for these polycyclic compounds indicates by analogy that the

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* *Discussion by Dr. D. C. Smith.*

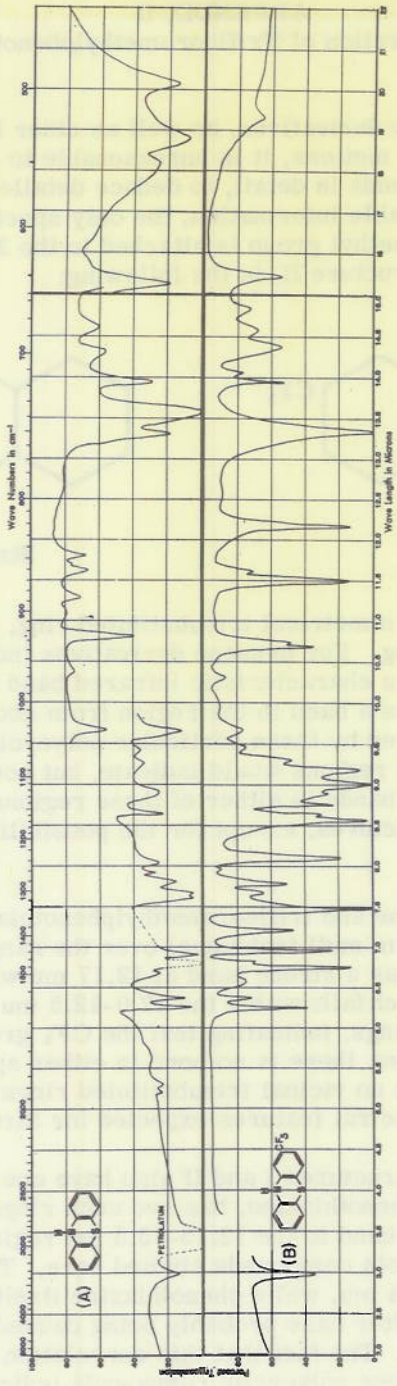

Figure 11 - Infrared spectrum of phenothiazine (A) and 2-trifluoromethylphenothiazine (B)

previous correlations for trisubstituted rings, upon which the identification of the subject compound as Structure I was based, may also be valid.

Although it has no bearing upon the present problem, it is of interest to note that it should be possible to identify the presence of the CF_3 group in this compound. According to previous work on benzotrifluorides, it appears that a CF_3 group attached to an aromatic ring always gives rise to a strong infrared band in each of the regions 7.40-7.50, 8.70-8.90, and near 15.2 mu. The compound, 2-trifluoromethylphenothiazine, has strong bands at 7.47 and 8.75 mu which are not present in phenothiazine, and both compounds have a band near 15.2 mu. Thus, the present data supports the previous conclusions, at least for two of the bands which characterize an aromatic CF_3 group.

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REFERENCES

1. Murphy, C. M. and Saunders, C. E., Petroleum Refiner 26, 479 (1947)
2. U. S. Naval Mission in Europe, Technical Report No. 146-5 "The Manufacture and Application of Lubricants in Germany."
3. U. S. Dept. of Interior, Bureau of Mines Information Circular I. C. 7370 "Report of the Investigation by the Fuels and Lubricants Team at the I. G. Farben-Industrie A. G. Leuna Works, Merseberg, Germany."
4. Ravner, H., Murphy, C. M., Jr., and Smith, N. L., "Phenothiazine-Type Antioxidants and Their Mode of Action," NRL Report No. 3546, 18 Jan. 1950.
5. Goldberg, I., Ber. 40, 4541 (1907)
6. Buu-Hoi, C., J. Chem. Soc., 672 (1949); Comp. Rend. 218, 648 (1944)
7. Bernthsen, A., Ber. 16, 2897 (1883)
8. Ullman, F., Ann. 355, 312 (1907)
9. Baltzly, R., Harfenist, M., and Webb, F. J., J. Am. Chem. Soc. 68, 2673 (1946)
10. Gilman, H. and Shirley, D. A., J. Am. Chem. Soc. 66, 891 and 1215 (1944)
11. Calcott, W. S., Carleton, P. W., and Mattison, E. I., U. S. Patent 2,085,736, 6 July 1937
12. Bernthsen, A., Ann. 230, 88 (1885)
13. Ford, G. M., Iowa State Coll. J. Sci. 12, 121 (1937); C. A. 32, 4943 (1938)
14. Whitmore, F. C., et. al., J. Am. Chem. Soc. 66, 725 (1944)
15. Barnett, E. D. and Smiles, S. J., J. Chem. Soc., 1253 (1909)
16. Bernthsen, L., Ber. 39, 1807 (1906)
17. Pesci, L., Gazz. chim. ital. 46, 103 (1916); C. A. 10, 2885 (1916)
18. De Eds, F. and Eddy, C. W., J. Am. Chem. Soc. 60, 1446 (1938)
19. Granick, S., Michaelis, L., and Schubert, M. P., J. Am. Chem. Soc. 62, 1802 (1940)
20. Houston, D. F., Kester, E. B., and De Eds, F., two papers presented at ACS meeting March 27 to April 1, 1949 at San Francisco, Cal.
21. Clemo, G. R. and McIlwain, H., J. Chem. Soc., 1991 (1934)

22. Cornelius, W., Chem. Ztg. 37, 198 (1914)

23. Buu-Hoi, C. and LeCocq, J., Rec. trav. chim. 64, 250 (1945)

24. Kehrmann, F., Ber. 48, 326 (1915)

25. Vesely, O., Misslin, E., Gressly, A., and Schild, L., Ann. 322, 46 (1902)

26. Kym, O., Ber. 23, 2458 (1890)

27. Cauquil, G. and Cassadevall, A., Compt. rend. 225, 578 (1947)

28. Pummerer, R. and Gassner, S., Ber. 46, 2322 (1913)

29. Bernthsen, A., Ber. 39, 1807 (1906)

30. Ris, C., Ber. 90, 2206 (1886)

31. Scholl, R. and Newberger, W., Monatsch. 39, 238 (1918)

32. German Patent 641,597; British Patent 475,621

33. Buu-Hoi, C. and Cagniant, P., Ber. 77, 121 (1944)

34. Rodgers, C. U. and Carson, B. B., J. Am. Chem. Soc. 69, 2910 (1947)

35. Thompson, H. W., J. Chem. Soc., 328 (1943)

36. Barnes, R. B., Anal. Chem. 20, 402 (1948)

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