[CONTRIBUTION FROM THE CHEMISTRY DIVISION, NAVAL RESEARCH LABORATORY]

SYNTHESIS OF PHENOTHIAZINE DERIVATIVES FOR USE AS ANTIOXIDANTS

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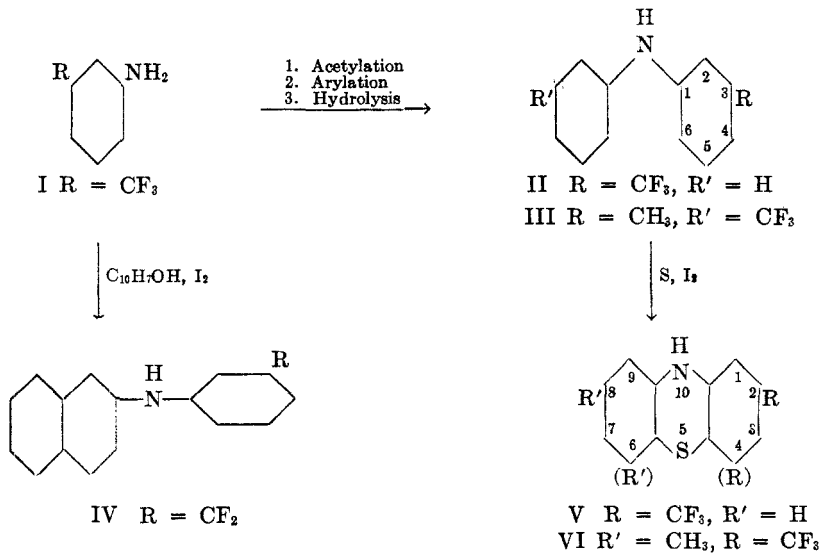
Received May 18, 1950

As a result of the interest in phenothiazine as an antioxidant for lubricant application, a project was initiated to synthesize phenothiazine derivatives of interest, to test them as antioxidants, and to study their mode of action.[1] Two objectives of the preparative phase of that investigation are described in this communication: first, the synthesis of some trifluoromethylated phenothiazines from the corresponding aromatic secondary amines, and secondly, the formation and cyclization of β-(10-phenothiazyl)propionic acid. The substituted propionic acid, previously prepared by Cauquil and Cassadevall,[2] was obtained by hydrolysis of the cyanoethylation product of phenothiazine.

Asymmetrical and substituted trifluoromethylated diarylamines provided the corresponding thiazine structures by an iodine-catalyzed modification of Bernthsen's fusion with sulfur (1). For the preparation of the aromatic secondary amines, either the convenient Buu-Hoï condensation of an aryl amine with an aryl hydroxy compound (2) or the Goldberg condensation of a substituted acetanilide with an aryl halide (3) was employed.

The commercially available *m*-trifluoromethylaniline (I)[3] served as convenient starting material for the preparation of 3-trifluoromethyldiphenylamine (II), 3-trifluoromethyl-3′-methyldiphenylamine (III), and 3-trifluoromethylphenyl-β-naphthylamine (IV). Consequently, the thionation products prepared in this investigation from the first two diarylamines must be 2- or 4-trifluoromethylphenothiazine (V) and 2- or 4-trifluoromethyl-6- or 8-methylphenothiazine (VI) depending on the orientation effect of sulfur bridging:



Gilman (4) and Baltzly (5) discussed the position problem with respect to metalation and acylation of phenothiazine, while Calcott (6) considered it for some fluorinated and trifluoromethylated methylene blue compounds and Buu-Hoï (7) for a methyl-substituted benzophenothiazine. The observations of these investigators indicate that position orientation varied with the formation and reactions of thiazines and that chemical methods of identification showed little promise. Since the exact position of the phenothiazine adduct is of considerable interest for inhibitor studies, it was decided to subject trifluoromethylphenothiazine to spectral examination.

Thompson (8) and Barnes (9) have shown that unsymmetrical trisubstituted benzene structures produce a characteristic infrared band in the region 12.0 to 12.5μ, while *vicinal*-trisubstituted benzene compounds produce bands in the retion from about 12.5 to 13.15μ. If these correlations are followed by 2- or 4-trifluoromethylphenothiazine then a strong band in either of these regions is indicative of the corresponding structure.

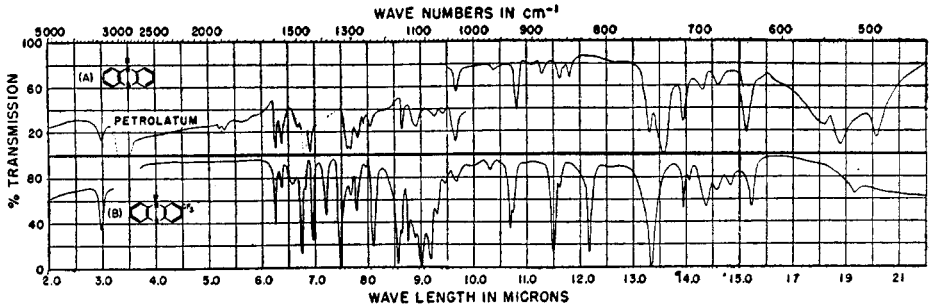


FIGURE 1. A. Infrared Spectrum of Phenothiazine. B. Infrared Spectrum of 2-Trifluoromethylphenothiazine.

The spectra of phenothiazine and trifluoromethylphenothiazine, studied in the solid phase (using the petroleum mull technique) over the range 2–22μ, are shown in Figure 1. It is seen that trifluoromethylphenothiazine has a strong band at 12.17 which is not in the phenothiazine spectrum, indicating that the CF_3 group is attached to the 2-position. Accordingly, the methyl and trifluoromethyl groups in the two phenothiazine compounds prepared by thionation reactions are provisionally assigned to positions 2 and 8. The presence of the sulfur atom seems to orientate the groups to the *para*-positions.

With the object of investigating the use of substituted propionic acids for the preparation of new types of thiazine compounds, the synthesis of β-(10-phenothiazyl)propionic acid (IX) was attempted. Although some or all of the reactions involved have been applied to other heterocyclic compounds (10, 11), apparently

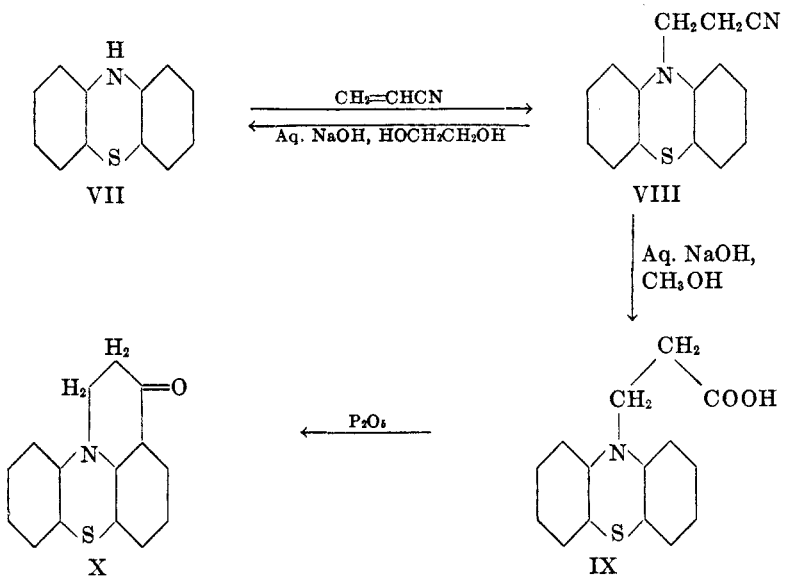
[1] An evaluation of the inhibitor properties of these compounds and a theoretical discussion of their mode of action will be discussed elsewhere.

[2] These authors reported (12) the preparation of this acid by the hydrolysis of the condensation product of ethyl β-bromopropionate with phenothiazine.

[3] Product of Hooker Electrochemical Company, Niagara Falls, N. Y.

no similar process has been described in the chemical and patent literature for phenothiazine.

The synthesis of β-(10-phenothiazyl)propionic acid (IX) *via* the hydrolysis of the cyanoethylation product of phenothiazine (VII), β-(10-phenothiazyl)-propionitrile (VIII), and subsequent cyclization of the substituted propionic acid readily provided 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*] phenothiazine (X):[4]



A vigorous but controllable reaction was initiated when a 40% solution of benzyltrimethylammonium hydroxide[5] was added to a mixture of 0.1 mole of phenothiazine and an excess of acrylonitrile; very efficient cooling was necessary when larger quantities of the reactants were used. The reaction product, β-(10-phenothiazyl)propionitrile, furnished the corresponding propionic acid on hydrolysis with an aqueous methanol-sodium hydroxide solution and subsequent acidification. Replacing the methanol with ethylene glycol resulted in the unexpected rupture of the hetero nitrogen-carbon bond, in addition to the action on the cyano group, liberating β-hydroxypropionic acid and phenothiazine. Apparently, under conditions specified for the reaction, the smaller fragment dehydrates readily, since only acrylic acid was isolated.

β-(10-Phenothiazyl)propionic acid was converted into the anhydride at the boiling point of dry xylene in the absence of a dehydrating agent. When boiled with phosphoric anhydride in benzene, the acid gave the desired ketone in 76% yield. The cyclic ketone was characterized by its phenylhydrazone and 2,4-dinitrophenylhydrazone.

The trifluoromethylated phenothiazines resemble the parent heterocyclic compound in color, crystalline structure, and tendency to discolor on exposure to

[4] Nomenclature recommended by Drs. L. T. Capell and A. M. Patterson.

[5] Triton B, product of Rohm and Haas Company, Philadelphia, Pa.

atmospheric conditions. Furthermore, the color phenomena of diarylamines and phenothiazines with concentrated sulfuric acid were observed with the trifluoromethylated derivatives prepared.

EXPERIMENTAL[6]

3-Trifluoromethyldiphenylamine (II). 3-Trifluoromethylaniline was first converted to the acetyl derivative with acetic anhydride. A mixture of 20.3 g. (0.1 mole) of 3-trifluoromethylacetanilide, m.p. 110°, and 31.4 g. (0.2 mole) of bromobenzene in 100 ml. of nitrobenzene was stirred under reflux for 21 hours in the presence of 15.0 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% yield (21.0 g.), 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, washed with alkali and water, dried over sodium sulfate, the solvent removed, and the residue distilled. 3-Trifluoromethyldiphenylamine distilled as a yellow liquid, b.p. 108–110° (0.3 mm.), n_D^{25} 1.5655 and weighed 10.6 g. (56%). A picrate crystallized from benzene in coarse yellow needles, m.p. 147°. The amine is steam-distillable.

Anal. Calc'd for $C_{13}H_{10}F_3N$: N, 5.90. Found: N, 5.90[7].

2-Trifluoromethylphenothiazine (V). To 7.0 g. (0.03 mole) of 3-trifluoromethyldiphenylamine was added 2.0 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 weighed 3.5 g. (44% yield) and was recrystallized from alcohol in 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. The color impurities of this thiazine can be removed by treatment with zinc dust.

Anal. Calc'd for $C_{13}H_8F_3NS$: C, 58.20; H, 3.16.
Found: C, 58.56, H, 3.22.

3-Trifluoromethyl-3'-methyldiphenylamine (III). A mixture of 50.3 g. (0.25 mole) of 3-trifluoromethylacetanilide, 85.5 g. (0.5 mole) of 3-bromotoluene, 33.0 g. of anhydrous potassium carbonate, 1.0 g. of cuprous bromide, and 300 ml. of dry nitrobenzene was heated under reflux for 18 hours. The nitrobenzene and unchanged 3-bromotoluene were steam-distilled, and the residue 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 alkali and water. The amine distilled as a yellow oil, b.p. 130–132° (1.0 mm.), n_D^{25} 1.5581 and weighed 24.0 g. (39%). The hydrochloride melted at 228° with decomposition.

Anal. Calc'd for $C_{14}H_{12}F_3N$: N, 5.58. Found: N, 5.92.

The *acetyl* derivative, prepared by boiling the amine with excess acetic anhydride for two hours, was obtained from *n*-hexane in the form of white crystals, m.p. 67–68°.

2-Trifluoromethyl-8-methylphenothiazine (VI). 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 charcoal and Filter-Cel, and recrystallized from benzene as yellow platelets, m.p. 227–228° in 52% yield (1.3 g.). In conc'd sulfuric acid, the thiazine gives a reddish-brown color.

Anal. Calc'd $C_{14}H_{10}F_3NS$: N, 4.98. Found: N, 4.98.

3-Trifluoromethylphenyl-β-naphthylamine (IV). A mixture of 72.0 g. (0.5 mole) of β-naphthol and 80.5 g. (0.5 mole) of 3-trifluoromethylaniline was heated under reflux for 24

[6] All melting and boiling points are uncorrected.

[7] Microanalyses performed by Oakwold Laboratories, Alexandria, Va.

hours in the presence of 0.5 g. of iodine. The dark oil was taken up in toluene, washed with alkali, and dried over sodium sulfate. After the removal of the solvent the residue was distilled *in vacuo*, b.p. 180–185° (2 mm.). The reddish-brown distillate (71.0 g.) solidified on cooling. Recrystallization from alcohol yielded white needles, m.p. 83–84°. No crystalline picrate was formed.

Anal. Calc'd for $C_{17}H_{12}F_3N$: C, 71.00; H, 4.18; N, 4.87.
Found: C, 70.64; H, 4.17; N, 5.22.

β-(10-Phenothiazyl)propionitrile (VIII). A mixture of 200 g. (1.0 mole) of phenothiazine[8] and 300 ml. of acrylonitrile was cooled in an ice-bath and treated with 3.0 ml. of a 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 vacuum-dried yielding 235 g. (93%) of crude product. Recrystallization from acetone gave 171 g. (73% recovery) of thick colorless needles, m.p. 158–159°. No picrate was formed. The nitrile was soluble in 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.

β-(10-Phenothiazyl)propionic acid (XI). The successful hydrolysis of the nitrile was accomplished by boiling a mixture of 25.0 g. (0.1 mole) of β-(10-phenothiazyl)propionitrile, 25.0 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. (65%), was recovered in the form of fine needles, m.p. 163°[9]; Neut. equiv., 272.0 (calc'd, 271.4).

An attempt to prepare the acid in ethylene glycol failed. A mixture of β-(10-phenothiazyl)propionitrile, 250 ml. of ethylene glycol, 25 g. of sodium hydroxide, and 40 ml. of water was boiled under reflux for 6.5 hours, cooled, acidified with dilute hydrochloric acid, washed with water, and finally 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 its methyl ester, b.p. 80°.

The anhydride of the acid precipitated from a solution of the acid in dry xylene at the boiling point, m.p. 228° (decomp.). The original acid was recovered from aqueous alkali solution by acidification.

2,3-Dihydro-3-keto-1H-pyrido [3,2,1-kl] phenothiazine (X). β-(10-Phenothiazyl)propionic acid (10 g., 0.04 mole) was treated with 50.0 g. of phosphoric anhydride in 200 ml. of dry benzene. The mixture was heated for one hour on a steam-bath and allowed to remain at room temperature overnight. The reaction product was treated with ice-water, washed with water, then with sodium carbonate solution, again with water, and dried over sodium sulfate. The solvent was removed and the residue taken up with alcohol, diluted with water and allowed to crystallize. Yield: 7.1 g. (76%). Recrystallization from alcohol gave yellow needles, m.p. 112–113°.

Anal. Calc'd for $C_{15}H_{11}NOS$: C, 71.07; H, 4.38; N, 5.53.
Found: C, 71.20; H, 4.25; N, 5.64.

The *2,4-dinitrophenylhydrazone* was obtained from alcohol as brick-red needles, m.p. 90°; the *phenylhydrazone* afforded yellow crystals from alcohol, m.p. 167°.

Anal. Calc'd for $C_{21}H_{17}N_3S$: C, 73.56; H, 4.99; N, 12.23.
Found: C, 73.56; H, 5.11; N, 12.34.

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to the following members of this laboratory; Dr. W. A. Zisman for many helpful discussions, Dr. D. C. Smith

[8] N.F. purified; manufactured by Dow Chemical Company, Midland, Mich.
[9] Reported m.p. 161° (12).

for interpretation of the infrared data, and L. W. Daasch for the infrared analyses.

SUMMARY

A series of seven phenothiazine derivatives and diarylamines were synthesized in a program designed to provide antioxidants of interest for lubricant application.

The aromatic secondary amines—3-trifluoromethyldiphenylamine, 3-trifluoromethyl - 3′ - methyldiphenylamine, 3 - trifluoromethylphenyl - β - naphthylamine —were prepared by condensation reactions with 3-trifluoromethylaniline. Thionation reactions converted two of the amines into the corresponding thiazine structures—2-trifluoromethylphenothiazine and 2-trifluoromethyl-8-methylphenothiazine.

Cyanoethylation of phenothiazine provided β-(10-phenothiazyl)propionitrile, which was hydrolyzed to the corresponding propionic acid. The acid readily cyclized to 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine.

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