N, 48.14. *Anal.* Calcd. for $C_3H_3Cl_2N_4$: C, 21.73; H, 1.22; Cl, 42.79; N, 33.96. Found: C, 24.08; H, 2.62; Cl, 36.58; N, 36.48.

Diethylamine and cyanuric fluoride. A solution of cyanuric fluoride (1.36 g., 10 mmoles) in tetrahydrofuran (5 ml.) was added to a stirred solution of diethylamine (5.1 g., 70 mmoles) in tetrahydrofuran (25 ml.) at 20° during 15 min. The reaction mixture was stirred for an additional 80 min. The tetrahydrofuran then was evaporated *in vacuo* (surrounding bath at 60°) to yield an oily residue. This was stirred for 15 min. with 50 ml. of water, extracted with ether, and the organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to yield a colorless solid. There was obtained 2,4-bis(diethylamino)-6-fluoro-*s*-triazine (1.77 g., 7.4 mmoles, 74% yield), m.p. 37–44°. A small amount of the material was sublimed (60°/0.5 mm.) to yield crystals, soften 37°, m.p. 44–45.5°.[10]

Anal. Calcd. for $C_{11}H_{20}FN_5$: C, 54.75; H, 8.35; F, 7.87; N, 29.03. Found: C, 54.79; H, 8.58; F, 8.08; N, 29.24.

Diethylamine and cyanuric chloride. The procedure was like that used for cyanuric fluoride except that (1.84 g., 10 mmoles) of cyanuric chloride was used. The oily solid was dissolved in chloroform and the chloroform extracted with water until the aqueous phase remained neutral. The organic layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield an oil which was taken to constant weight (25°/0.5 mm.). There was obtained crude 2,4-bis-(diethylamino)-6-chloro-*s*-triazine, (2.57 g., 10 mmoles, 100%).[2a]

Anal. Calcd. for $C_{11}H_{20}ClN_5$: C, 51.24; H, 7.82; Cl, 13.75; N, 27.17. Found: C, 50.67; H, 8.05; Cl, 12.72; N, 26.19.

Aniline and cyanuric fluoride. Cyanuric fluoride (1.36 g., 10 mmoles) in tetrahydrofuran (10 ml.) was added over 5 min. to a stirred solution of aniline (5.58 g., 60 mmoles) in tetrahydrofuran (25 ml.) at room temperature. The reaction mixture was stirred for 2 hr. The tetrahydrofuran was evaporated *in vacuo* to yield a white solid which was triturated thoroughly with 5% HCl. The solid was filtered, washed with water until the filtrate remained neutral, and then dried *in vacuo* (80°/20 mm.) to constant weight. There was obtained crude triphenylmelamine (3.53 g., 10 mmole, 100%), soften 215°, m.p. 222–227°, (lit. m.p. 229–231°).[2b] A small sample was sublimed (140°/0.5 mm.) to yield a white crystalline sublimate I, m.p. 222–227°,[11] and a small amount of non-sublimated amorphous tan solid II, m.p. 300°.

Anal. Calcd. for I, $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71. Found: C, 69.74; H, 5.47; N, 19.98; F. 0.00.

Aniline and cyanuric chloride. The procedure and work-up followed those used for cyanuric fluoride except that (1.84 g., 10 mmoles) of cyanuric chloride was used. The white solid was dried at (25°/0.5 mm.) to constant weight. There was obtained crude 2,4-bis(phenylamino)-6-chloro-*s*-triazine (3.05 g., 10 mmoles, 100%), m.p. 187–191°, (lit. m.p. 199–201°).[2a]

Anal. Calcd. for $C_{15}H_{13}ClN_5$: C, 60.49; H, 4.06; Cl, 11.91, N, 23.52. Found: C, 61.99; H, 4.49; Cl, 9.16; N, 22.89.

Water and cyanuric fluoride. A solution of cyanuric fluoride (2.72 g., 20 mmoles) in tetrahydrofuran (10 ml.) was added to a stirred solution of water (2.0 g., 110 mmoles) in tetrahydrofuran (25 ml.) at 0° over 10 min. The tetrahydrofuran was evaporated at room temperature *in vacuo* to yield a white solid which was dried *in vacuo* (25°/0.5 mm.) to constant weight. There was obtained cyanuric acid (2.45 g., 18.8 mmoles, 94%).

Anal. Calcd. for $C_3H_3N_3O_3$: C, 27.91; H, 2.34; N, 32.55. Found: C, 27.74; H, 2.56; N, 32.47; F, 0.00.

Water and cyanuric chloride. The procedure and work-up were those used for cyanuric fluoride except that (3.69 g., 20 mmoles) of cyanuric chloride was used. There was obtained a white solid, a mixture of cyanuric chloride and cyanuric acid[12] (3.33 g.).

Anal. Calcd. for $C_3Cl_3N_3$: C, 19.54; Cl, 57.70; N, 22.79. Found: C, 20.76; H, 3.07; Cl, 48.07; N, 23.25.

Methanol and cyanuric fluoride. A solution of cyanuric fluoride (2.78 g., 20 mmoles) in tetrahydrofuran (10 ml.) was added to a stirred mixture of anhydrous potassium carbonate (8.2 g., 60 mmoles) and methanol (25 ml.) at 10° over 5 min. The reaction mixture was stirred for 2 hr. at room temperature, filtered, and the residue I was washed with chloroform. The chloroform was combined with the filtrate; the resulting mixture was evaporated *in vacuo* at room temperature to yield a white solid II. The solid II was triturated with cold water (50 ml.), pressed dry on a filter, and dried to constant weight *in vacuo* (95°/20 mm.). There was obtained 2,4,6-tris(methoxy)-*s*-triazine (2.65 g., 15.5 moles, 77%), m.p. 133–135.5°, (lit. m.p. 134–136°).[2c]

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.29; N, 24.55. Found: C, 42.04; H, 5.44; N, 24.42.

Methanol and cyanuric chloride. The procedure and work-up were those used for cyanuric fluoride except (2.68 g., 20 mmoles) of cyanuric chloride was used. The white solid was dried to constant weight on a suction filter with a rubber dam. There was obtained crude 2,4,6-tris(methoxy)-*s*-triazine (2.03 g., 12 mmoles, 60%), m.p. 94–120° (lit. m.p. 134–136°).[2c]

Anal. Calcd. for $C_6H_6ClN_3O_2$: C, 34.20; H, 3.45; Cl, 20.20, N, 23.93. Found: C, 39.43; H, 4.84; Cl, 5.43; N, 21.45.

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CHEMICAL RESEARCH DEPARTMENT
RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

(10) All melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected.

(11) Repeated recrystallization from hot 1-butanol did not improve the purity of the product.

(12) The infrared spectrum of the solid (KBr disk) contained all the bands of cyanuric chloride in addition to those of cyanuric acid.

Synthesis of 2-Chlorophenothiazine *via* a Smiles Rearrangement[1]

ROBERT J. GALBREATH[2] AND ROBERT K. INGHAM

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2-Chlorophenothiazine (I) is the parent compound of chloropromazine [2-chloro-10-(3-dimethylaminopropyl)phenothiazine] (II) and of related biologically active substances. The principal method of preparation of 2-chlorophenothiazine involves the reaction of 3-chlorodiphenylamine with sulfur.[3] Both the 2-chloro and 4-chloro isomers are obtained from this reaction; the 2-chloro derivative

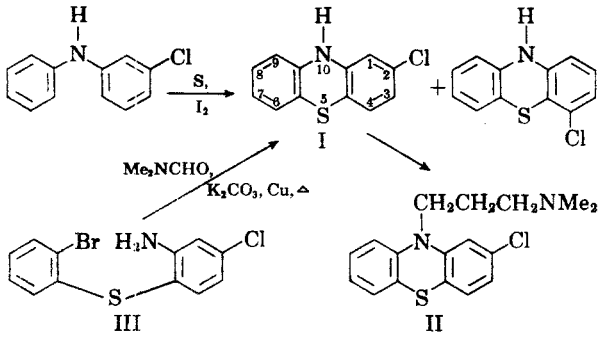
(1) Abstracted from an undergraduate research project of Robert J. Galbreath, Ohio University, 1957.

(2) Present address: School of Medicine and Dentistry, The University of Rochester.

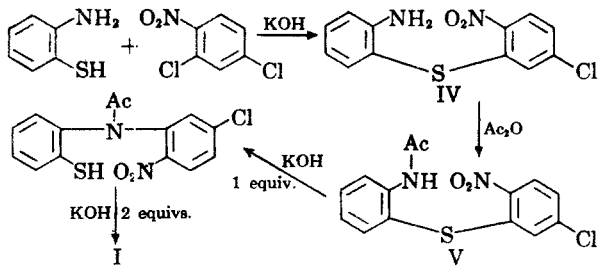
(3) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. rend.*, **235**, 59 (1952); P. Charpentier, U. S. Patent **2,645,640** [*Chem. Abstr.*, **49**, 3268 (1955)]; British Patent **716,205** [*Chem. Abstr.*, **50**, 1929 (1956)].

is the dominant isomer, although no yields appear in the reports.

Recently, a synthesis of 2-chlorophenothiazine from 2-bromophenyl 2-amino-4-chlorophenyl sulfide (III) has been reported.[4]



Our synthesis of 2-chlorophenothiazine involves the following reactions:



A number of halophenothiazines have been prepared *via* the Smiles rearrangement and it is rather surprising that the synthesis of the important 2-chloro compound by this method has not been reported. Related compounds which have been prepared in this manner include the 3-chloro-,[5,6] 3-bromo-,[7] 3-iodo-,[7] and 3-fluorophenothiazine.[8]

Roe and Little[8] have attempted the preparation of 2-fluorophenothiazine from 2-formamidophenyl 5-fluoro-2-nitrophenyl sulfide. The desired sulfide was obtained but a subsequent rearrangement was not successful; an unidentified substance containing no fluorine was the only product isolated.

Similarly, an attempt to prepare 2-bromophenothiazine from 2-acetamido-4-bromophenyl 2-nitrophenyl sulfide failed; the sulfide could not be made to undergo a Smiles rearrangement.[9] An attempt to deaminate 2-bromo-7-aminophenothiazine was also unsuccessful.[9]

Recently, Farrington and Warburton[10] attempted the preparation of 2,8-dichlorophenothiazine by rearrangement and ring closure of 2-acetamido-4-chlorophenyl 5-chloro-2-nitrophenyl sulfide; rearrangement occurred but heating with sodium hydroxide, sodium ethoxide, or sodium isopropoxide in various solvents failed to give the phenothiazine compound. These authors concluded that a chlorine atom *ortho* or *para* to the nitro group interferes with ring closure.

Similarly, Fujii[11] reported that 2-chloro-10-methylphenothiazine could not be obtained by subjecting 2-methylamino-4-chlorophenyl 2-nitrophenyl sulfide to Smiles rearrangement conditions.

The above-mentioned work plus other literature reports[12] left no doubt that the nucleophilic attack on 2,4-dichloronitrobenzene would take place preferentially at the 2-position. Indeed, the 2-aminophenyl 5-chloro-2-nitrophenyl sulfide (IV) was obtained in 78% yield. Acetylation occurred readily and, in spite of the discouraging reports mentioned above, rearrangement and subsequent ring closure were accomplished to give the desired 2-chlorophenothiazine.

EXPERIMENTAL[13]

2,4-Dichloronitrobenzene. There are numerous references in the literature to the preparation of 2,4-dichloronitrobenzene; almost all reports conclude that the method of choice is the nitration of *m*-dichlorobenzene. Since all of the procedures for this reaction are somewhat short on detail,[14] the following procedure is included.

To 75.0 g. (0.51 mole) of *m*-dichlorobenzene at 0° was added dropwise, with stirring, 140 ml. of fuming nitric acid (sp. gr. 1.50). The mixture was stirred at 0° for 1 hr.; it was then slowly warmed to 65° and maintained at this temperature for 20 min. After pouring the mixture into ice water, the resulting light yellow solid was removed by filtration and washed with water. This material was recrystallized from ethanol; the filtrate was twice heated, diluted and cooled to give additional product. The light yellow needles were washed with cold petroleum ether (b.p. 30–60°) and dried to give a total yield of 80.5 g. (82%) of 2,4-dichloronitrobenzene melting at 31.5–32°.

(4) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Patent 2,769,002 [*Chem. Abstr.*, **51**, 6709 (1957)].

(5) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).

(6) H. L. Yale, *J. Am. Chem. Soc.*, **77**, 2270 (1955).

(7) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Australian J. Chem.*, **8**, 252 (1955) [*Chem. Abstr.*, **50**, 3449 (1956)].

(8) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955).

(9) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(10) K. J. Farrington and W. K. Warburton, *Australian J. Chem.*, **9**, 480 (1956) [*Chem. Abstr.*, **51**, 4379 (1947)].

(11) K. Fujii, *J. Pharm. Soc., Japan*, **77**, 3 (1957) [*Chem. Abstr.*, **51**, 8756 (1957)].

(12) For a review of the reaction of nucleophilic reagents with 2,4-dihalonitrobenzenes, see J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 5051 (1955); see also, M. W. J. De Mooy, *Rec. trav. chim.*, **35**, 5 (1915) and J. F. Bunnett, *Quart. Revs.*, **11**, 1 (1958).

(13) All melting points are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) A. F. Holleman, *Rec. trav. chim.*, **23**, 369 (1904); E. Roberts and E. E. Turner, *J. Chem. Soc.*, **127**, 2004 (1925); L. M. F. van de Lande, *Rec. trav. chim.*, **51**, 98 (1932); and C. C. Price and C. A. Sears, *J. Am. Chem. Soc.*, **75**, 3276 (1953).

2-Aminophenyl 5-chloro-2-nitrophenyl sulfide (IV). To a solution of 38.4 g. (0.20 mole) of 2,4-dichloronitrobenzene and 25.2 g. (0.20 mole) of 2-aminobenzenethiol in 670 ml. of isopropyl alcohol was added dropwise, with stirring, a solution of 13.2 g. of 85% potassium hydroxide in 30 ml. of 95% ethanol. The mixture was then refluxed for 3 hr. After refluxing, a bright orange precipitate was present in the mixture.

The mixture was then evaporated, under vacuum, to dryness; the residual solid was washed well with water and air-dried. The crude product melted from 124–132°. Recrystallization from absolute ethanol gave 43.8 g. (78%) of orange crystals, melting at 132–133.5°. This material was employed in the subsequent experiment without further purification. An analytical sample of the 2-aminophenyl 5-chloro-2-nitrophenyl sulfide melting at 135–136° was obtained by an additional recrystallization from absolute ethanol.

Anal. Calcd. for $C_{12}H_9ClN_2O_2S$: Cl, 12.63; N, 9.98; S, 11.42. Found: Cl, 12.57; N, 9.93; S, 11.52.

2-Acetamidophenyl 5-chloro-2-nitrophenyl sulfide (V). A mixture of 16.3 g. (0.058 mole) of the above sulfide, 110 ml. of acetic anhydride, 7 ml. of pyridine, and 2 g. of charcoal was heated for 2 hr. on a steam bath and filtered hot. The pale yellow filtrate was concentrated to dryness, leaving 17.4 g. (93%) of a bright yellow solid. The material melted from 143–150° and was found suitable for the next experiment without further purification.

Recrystallization of a portion of the crude 2-acetamidophenyl 5-chloro-2-nitrophenyl sulfide, first from benzene and then from absolute ethanol, gave an analytical sample as pale yellow needles, m.p. 154.4–155°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_3S$: Cl, 10.99; N, 8.68; S, 9.93. Found: Cl, 10.80; N, 8.77; S, 9.91.

2-Chlorophenothiazine (I). To 888 ml. of acetone was added a solution of 6.8 g. of 85% potassium hydroxide in 51 ml. of 95% ethanol. After this mixture had been stirred and diffused with nitrogen for 15 min., 16.1 g. (0.05 mole) of the crude acetamido derivative was added and the solution was refluxed for 3 hr. Approximately 600 ml. of the acetone was removed by distillation under a nitrogen atmosphere; 500 ml. of petroleum ether (b.p. 90–120°), and 700 ml. of water were then added to the residual liquid. A small amount of insoluble material present was removed by filtration. After separation of the two layers, the aqueous layer was washed with an additional 200 ml. of petroleum ether and the organic layer was washed with 200 ml. of water. The combined petroleum ether solutions were dried over magnesium sulfate and reduced in volume to 60 ml. by distillation. Cooling, filtering, and washing the resulting precipitate with cold petroleum ether (b.p. 20–40°) gave 5.5 g. of a brown solid which melted from 180–193°, with prior shrinkage. This material was recrystallized (Norit) from xylene to give 4.3 g. (37%) of pale yellow crystals melting at 194.5–196.5°. An additional recrystallization from xylene gave 3.6 g. of almost colorless crystals, m.p. 196–197°. A mixture melting point with an authentic sample[15] of 2-chlorophenothiazine showed no depression; also, the infrared spectra[16] of the two specimens were identical.

DEPARTMENT OF CHEMISTRY
OHIO UNIVERSITY
ATHENS, OHIO

(15) The authors wish to express their appreciation to Dr. Eugene L. Wittle, Research Laboratories, Parke, Davis & Co., Detroit, Mich., who generously supplied a sample of 2-chlorophenothiazine.

(16) The authors acknowledge with gratitude the financial aid provided by the National Science Foundation for the purchase of the Perkin-Elmer Model 21 infrared spectrophotometer used in this study (NSF-G3912).

Tris(*o*-methoxymethylphenyl)phosphine

R. L. LETSINGER, J. R. NAZY,[1] AND A. S. HUSSEY

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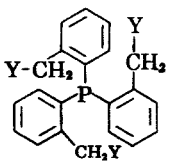
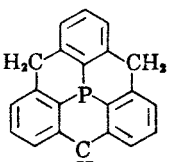
The intramolecular alkylation of the phosphine I or II would lead to the formation of III, an interesting new type of arylphosphine.



I, Y = CH_3O–
II, Y = Cl



III

While electrophilic substitution in the aromatic rings of triphenylphosphine is difficult, the nitration of triphenylphosphine to tris(*m*-nitrophenyl)phosphine oxide has been accomplished.[2] Further, the intramolecular alkylation of I would involve a reaction-assisting six-membered cyclic transition state. Accordingly, we have examined the effect of acids on phosphine I, using reagents ranging from formic acid, sulfuric acid in acetic acid, liquid hydrogen fluoride, stannic chloride, and aluminum chloride to concentrated sulfuric acid. All attempts to effect cyclization of I to III, however, have been unsuccessful. Some tris(*o*-methoxymethylphenyl)-phosphine oxide was recovered from a run employing aluminum chloride in nitromethane. Unreacted I and intractable tars were the only materials isolated from the other reactions.

Phosphine I was prepared by the reaction of *o*-lithiobenzyl methyl ether with phosphorus trichloride, the lithium reagent having been obtained by interchange between *n*-butyllithium and *o*-bromobenzyl methyl ether.[3] The phosphine reacted normally with hydrogen peroxide and with iodine to give the phosphine oxide, and with methyl iodide to give the methylphosphonium iodide.

Cleavage of the ether functions with boron trichloride[4] furnished tris(*o*-chloromethylphenyl)phosphine, II. Eighty-five percent of II was recovered unchanged from a reaction in liquid hydrogen fluoride. Aluminum chloride in nitromethane, however, converted II to tris(*o*-chloromethylphenyl)phosphine oxide (87%).[5] There was no indication that III was formed in either case.

(1) National Science Foundation Fellow.

(2) F. Challenger and J. Wilkinson, *J. Chem. Soc.*, 125, 2675 (1924).

(3) The corresponding Grignard reagent has been described by F. Holliman and F. G. Mann, *J. Chem. Soc.*, 1634 (1947).

(4) W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 1486 (1952).

(5) The oxidizing agent may have been air. Triphenylphosphine is oxidized in air in the presence of aluminum chloride to triphenylphosphine oxide; D. R. Lyon and F. G. Mann, *J. Chem. Soc.*, 666 (1942).