[CONTRIBUTION FROM THE CHEMISTRY DIVISION, NAVAL RESEARCH LABORATORY]

FORMATION AND OXIDATION OF SOME PHENOTHIAZINE DERIVATIVES

NATHAN L. SMITH

Received September 28, 1950

A number of phenothiazine derivatives were prepared in a search for new structures with better antioxidant characteristics than the parent heterocyclic compound (1). In this connection some trifluoromethylated diarylamines and phenothiazines, together with the formation and cyclization of 10-phenothiazylpropionic acid were recently reported (2). The present paper discribes new halogenated and alkylated phenothiazines and their amine precursors, in addition to the formation of sulfones from several of these phenothiazines.

N-*p*-Fluorophenyl-2-naphthylamine was prepared by the reaction of 2-naphthol with 4-fluoroaniline using the method of Sakom (3); while 3,3′-bis(trifluoromethyl)diphenylamine was obtained by the condensation of 3-trifluoromethylacetanilide and 3-bromobenzotrifluoride, and 2-trifluoromethyl-4,4′-difluorodiphenylamine was prepared from 4-bromofluorobenzene and 2-trifluoromethyl-4-fluoroacetanilide by the method of Goldberg (4).

Thionation reactions, using the iodine-catalyzed sulfur fusion method (3), produced 3-fluorophenothiazine and 3,7-bis(1,1,3,3-tetramethylbutyl)phenothiazine from the corresponding substituted diphenylamines in fair yields. No improvement in the yield of 3,7-bis(1,1,3,3-tetramethylbutyl)phenothiazine was obtained when soluble sulfur was substituted for insoluble sulfur in the fusion process.

3,7-Bis(1,1,3,3-tetramethylbutyl)phenothiazine and other previously reported phenothiazines (2) were readily converted in good yields to sulfones by the action of 30% hydrogen peroxide in glacial acetic acid. The identity of the sulfones of 10-phenothiazylpropionitrile and 10-phenothiazylpropionic acid was established by cleavage reactions with the formation of phenothiazine-5-dioxide; the nitrile reacted readily with alcoholic sodium hydroxide, whereas the acid necessitated the action of hydriodic acid.

The compounds described under Experimental are listed in the chart given below.

EXPERIMENTAL[1]

N-p-Fluorophenyl-2-naphthylamine (I). A mixture of 7.5 g. (0.07 mole) of 4-fluoroaniline, 10.0 g. (0.07 mole) of 2-naphthol, and 0.1 g. of iodine was refluxed for 21 hours. After cooling, the reaction product was dissolved in ethanol, precipitated by dilution with water, and washed thoroughly with water. The crude product weighed 17.0 g. (93%) and was purified by recrystallization from dilute ethanol, m.p. 86–87° (melting point block, corr.).

Anal. Calc'd for $C_{16}H_{12}FN$: C, 80.80; H, 5.10; N, 5.92.

Found: C, 80.60; H, 4.90; N, 6.11.[2]

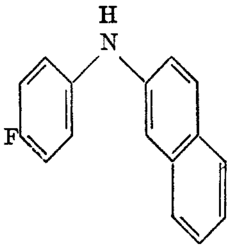
---

[1] Melting points and boiling points are uncorrected unless otherwise noted.

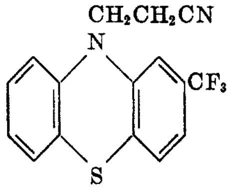
[2] Microanalyses performed by Oakwold Laboratories, Alexandria, Va.

3,3'-Bis(trifluoromethyl)diphenylamine (II). 3-Bromobenzotrifluoride, 79.0 g. (0.24 mole), and 70.0 g. (0.24 mole) of 3-trifluoroacetanilide were stirred under reflux in 300 ml. of nitrobenzene for 30 hours in the presence of anhydrous potassium carbonate and 1.0 g. of cuprous bromide, after which the excess 3-bromobenzotrifluoride and nitrobenzene were removed by steam. The residue was washed thoroughly with water, extracted with 300 ml. of alcohol, and the solution refluxed for four hours after the addition of 75 ml. of concentrated hydrochloric acid. The reaction mixture was made alkaline to litmus, extracted with ether and the ether removed by distillation. The product was recovered as a yellow liquid, b.p. 137–140° at 3.0 mm., n_D^{25} 1.5138 and weighed 32.0 g. (28% over-all). When dissolved in concentrated sulfuric acid, the amine produced a yellow color which upon the addition of nitric acid changed to green and then brown.

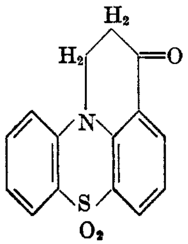
CHART I



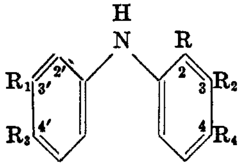
I



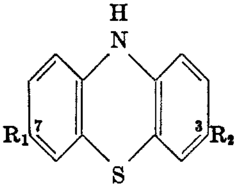
VIII



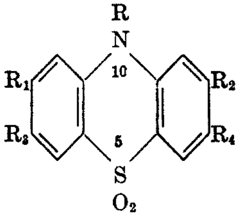
IX



II. $R = R_3 = R_4 = H, R_1 = R_2 = CF_3$
III. $R = CF_3, R_1 = R_2 = H, R_3 = R_4 = F$
IV. $R = R_1 = R_2 = R_3 = H, R_4 = F$



V. $R_1 = H, R_2 = F$
VI. $R_1 = R_2 = C_8H_{17}$



VII. $R = R_1 = R_2 = H, R_3 = R_4 = C_8H_{17}$
X. $R_1 = R_2 = R_3 = R_4 = H, R = CH_2CH_2CN$
XI. $R_1 = R_2 = R_3 = R_4 = H, R = CH_2CH_2CO_2H$

Anal. Calc'd for $C_{14}H_9F_6N$: N, 4.60. Found: N, 4.87.

2-Trifluoromethyl-4,4'-difluorodiphenylamine (III). 4-Bromofluorobenzene (25.0 g., 0.14 mole), and 22.1 g. (0.1 mole) of 2-trifluoromethyl-4-fluoroacetanilide (m.p. 120–121.5°) in 100 ml. of nitrobenzene were stirred under reflux for 20 hours in the presence of 20.0 g. of anhydrous potassium carbonate, 1.0 g. of copper powder, and 1.0 g. of cuprous bromide, after which the unchanged 4-bromofluorobenzene and nitrobenzene were removed by steam.

The residue was washed thoroughly with water, taken up with ethanol, filtered, the solution concentrated to 100 ml., then treated with 30 ml. of concentrated hydrochloric acid and refluxed for four hours. The product was poured into ice-water, extracted with ether, dried, the ether removed, and the residue distilled, b.p. 146–148° at 0.8 mm., n_D^{25} 1.5210. The yellow oil weighed 4.8 g. (19% over-all). The amine imparts a green color to concentrated sulfuric acid which changes to red upon the addition of nitric acid.

Anal. Calc'd for $C_{13}H_8F_5N$: N, 5.11. Found: N, 4.93.

4-Fluorodiphenylamine (IV). This compound, b.p. 130–131° at 1.5 mm., m.p. 34°, previously reported by Leonard and Sutton (5), was likewise prepared by the method of Goldberg (4).

3-Fluorophenothiazine (V). A mixture of 1.0 g. of 4-fluorodiphenylamine, 0.25 g. of sulfur, and 0.1 g. of iodine was heated in an oil-bath at 150-160° for an hour. The crude product was extracted with benzene, decolorized with charcoal (Filter-cel), filtered, and crystallized. Recrystallization from ethanol yielded 0.3 g. (39%) of yellow platelets melting at 176–177°. No picrate was formed. In concentrated sulfuric acid the compound produced a reddish-brown color which remained unchanged on dilution with water or the addition of nitric acid.

Anal. Calc'd for $C_{12}H_8FNS$: C, 66.40; H, 3.71; N, 6.45.
Found: C, 66.27; H, 3.90; N, 6.41.

3,7-Bis(1,1,3,3-tetramethylbutyl)phenothiazine (VI). *p,p'*-Bis(1,1,3,3-tetramethylbutyl) diphenylamine,[3] 2.0 g., was fused with 0.25 g. of insoluble sulfur[4] in the presence of 0.1 g. of iodine at 170° for 45 min. The reaction product was taken up in benzene and chromatographed on activated alumina by the procedure described by Huston, Kester, and DeEds (6). The crude product, isolated as a red crystalline mass, yielded 0.7 g. (31%) of yellow needles melting at 162–163° after recrystallization from cold petroleum ether (30–65°). A picrate, m.p. 154°, was obtained from ethanol. In concentrated sulfuric acid the compound produced a wine color which remained unchanged by the addition of nitric acid.

Substituting soluble sulfur[5] for the insoluble form in the above reaction gave the same yield of product.

Anal. Calc'd for $C_{28}H_{41}NS$: C, 79.40; H, 9.75; N, 3.31.
Found: C, 79.63; H, 9.45; N, 3.42.

3,7-Bis(1,1,3,3-tetramethylbutyl)phenothiazine-5-dioxide (VII). A mixture of 1.0 g. of VI, 30 ml. of glacial acetic acid, and 15.0 ml. of 30% hydrogen peroxide was refluxed for an hour, then poured into ice-water, filtered, and crystallized from ethanol. Recrystallization from ethanol yielded 0.5 g. (47%) of peach-colored needles, m.p. 294–295° (decomp.).

Anal. Calc'd for $C_{28}H_{41}NO_2S$: C, 73.79; H, 9.09; H, 3.07.
Found: C, 73.75; H, 8.78; N, 3.30.

2-Trifluoromethyl-β-(10-phenothiazyl)propionitrile (VIII). To a stirred mixture of 5.0 g. of 2-trifluoromethylphenothiazine (2) and 7.5 ml. of acrylonitrile was added 0.5 ml. of a 40% solution of benzyltrimethylammonium hydroxide. The reaction began in five minutes as evidenced by the sudden evolution of heat, and was brought to completion by warming on a steam-bath for an hour. The crystalline mass formed upon cooling was twice recrystallized from acetone affording 4.0 g. (67%) of white needles, m.p. 159.5–160.0°.

Anal. Calc'd for $C_{16}H_{11}F_3N_2S$: N, 8.74; S, 10.00.
Found: N, 8.56; S, 10.33.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenothiazine-7-dioxide (IX). This compound was prepared as usual from 0.5 g. of 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine,

---

[3] Recrystallized from *n*-hexane, m.p. 101–102°; acetyl derivative, m.p. 120–121°. Compound and information regarding structure obtained through the courtesy of B. F. Goodrich Chemical Company, Cleveland, Ohio.

[4] Sublimed, U.S.P., product of J. T. Baker Chemical Co., Phillipsburg, N. J.

[5] Standard sample of soluble sulfur, National Bureau of Standards, Washington 25, D. C.

15.0 ml. of glacial acetic acid, and 5.0 ml. of hydrogen peroxide. The product weighed 0.22 g. (39%) and crystallized from ethanol in tan needles, m.p. 195–196°.

Anal. Calc'd for $C_{15}H_{11}NO_3S$: N, 4.91. Found: N, 5.21.

β-(10-Phenothiazyl)propionitrile-5-dioxide (X). The white crystalline product, prepared from 1.00 g. of β-(10-phenothiazyl)propionitrile (2) by the procedure for IX, weighed 1.05 g. (94%) and melted at 233–234° after two recrystallizations from benzene. It also crystallized readily from acetonitrile.

Anal. Calc'd for $C_{15}H_{12}N_2O_2S$: N, 9.85. Found: N, 9.59.

Cleavage of β-(10-phenothiazyl)propionitrile-5-dioxide. A mixture of 1.0 g. of the dioxide, 20 ml. of methanol, and 20 ml. of 10% sodium hydroxide was refluxed for 9.5 hours. The methanol was distilled from the reaction mixture, the residue acidified with dilute hydrochloric acid, filtered, and the product recrystallized from ethanol, m.p. 160–161°. A mixed m.p. with an authentic sample of phenothiazine-5-dioxide, m.p. 160–161°, prepared from 10-ethylphenothiazine-5-dioxide showed no depression.

β-(10-phenothiazyl)propionic acid-5-dioxide (XI). By the procedure described for the preparation of IX, a quantitative yield of salmon-colored needles was obtained from β-(10-phenothiazyl)propionic acid. Recrystallization from dilute ethanol afforded white needles, m.p. 189.5–190.0°.

Anal. Calc'd for $C_{15}H_{13}NO_3S$: N, 4.87. Found: N, 4.78.

Cleavage of β-(10-phenothiazyl)propionic acid-5-dioxide. A mixture of redistilled hydriodic acid and XI was refluxed for four hours, then poured into ice-water, filtered, and crystallized from ethanol, m.p. 160–161°; mixed m.p. with an authentic sample of the dioxide showed no depression.

An attempt to rupture the substituted propionic acid failed under the conditions described for the nitrile.

Acknowledgments. The author wishes to thank Dr. G. C. Finger for supplying 4-fluoroacetanilide and 2-trifluoromethyl-4-fluoracetanilide, and Dr. W. E. Weaver for 3-bromobenzotrifluoride. It is a pleasure to acknowledge the helpful private correspondence with Dr. A. M. Patterson on the nomenclature of some of the phenothiazine compounds.

WASHINGTON 25, D. C.

REFERENCES

(1) MURPHY, RAVNER, AND SMITH, *Ind. Eng. Chem.*, **42**, 2479 (1950).
(2) SMITH, *J. Org. Chem.*, **15**, 1125 (1950).
(3) KNOEVENAGEL, *J. prakt. Chem.*, **197**, 1 (1914).
(4) GOLDBERG, *Ber.*, **40**, 4541 (1907).
(5) LEONARD AND SUTTON, *J. Am. Chem. Soc.*, **70**, 1564 (1948).
(6) HUSTON, KESTER, AND DEEDS, *J. Am. Chem. Soc.*, **71**, 3819 (1949).