[Contribution from the Venable Chemical Laboratory of the University of North Carolina]

The Preparation of Some Fluorophenothiazines[1]

ARTHUR ROE, JOHN A. MONTGOMERY,[2] WILLIS A. YARNALL,[2] AND V. A. HOYLE, JR.[2]

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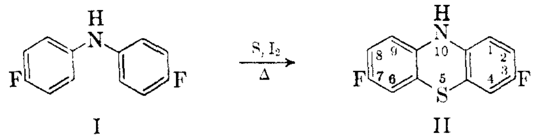
Four new fluorophenothiazines are reported: they are 2,7-difluoro-, 3,7-difluoro-, 2,8-difluoro-, and 8-fluoro-3,4-benzophenothiazine, and they were prepared by thionation of the corresponding diphenylamines. Attempts were made to prepare several other fluoro- and trifluoromethyl-phenothiazines. A number of new fluorodiarylamines and other intermediates are reported.

When this work was undertaken, the only fluorophenothiazines known were 3-fluoro-, 2-trifluoromethyl-, and 2-trifluoromethyl-8-methylphenothiazine reported by Smith.[3,4] This paper reports the preparation of four and the attempted preparation of nine new phenothiazines, together with the preparation of a number of new intermediates involved in the syntheses; others are reported in an accompanying paper.[5]

One of the usual methods of preparing phenothiazines is the reaction of an appropriately substituted diphenylamine with sulfur[6] and a catalyst, such as iodine;[7] hydrogen sulfide is evolved. The reaction temperature is usually between 180–230° and the time varies from a few minutes to several hours; in some cases both time and temperature are critical. This method is illustrated in the accompanying equation showing the formation of 3,7-difluorophenothiazine (II) from 4,4′-difluorodiphenylamine (I). The four new phenothiazines here reported were made by this method. They are 2,7-difluorophenothiazine (from 3,4′-difluorodiphenylamine), 2,8-difluorophenothiazine (from 3,3′-difluorodiphenylamine), 3,7-difluorophenothiazine (from 4,4′-difluorodiphenylamine), and 8-fluoro-3,4-benzophenothiazine [from N-(3-fluorophenyl)-2-naphthylamine].



I

II

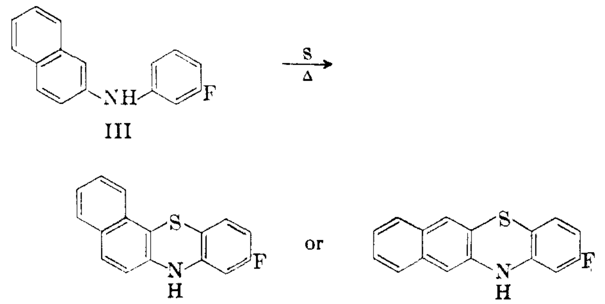
The structures were assigned the phenothiazines obtained from 3,3′-difluoro-, and 3,4′-difluorodiphenylamine, and from N-(3-fluorophenyl)-2-naphthylamine on the assumption that the sulfur ring closure would take place *para* rather than *ortho* to fluorine; reasons for this are discussed elsewhere.[5]

The diphenylamines from which no phenothiazines were isolated were the following:

2,2′-Difluorodiphenylamine
3,3′,4,4′-Tetrafluorodiphenylamine
3-Trifluoromethyl-4′-fluorodipenylamine
4,4′-bis(trifluoromethyl)diphenylamine
N-(3-Fluorophenyl)-1-napthylamine
N-(4-Fluorophenyl)-1-naphthylamine
N-(4-Fluorophenyl)-2-naphthylamine
N-Phenyl-4-fluoro-1-naphthylamine

In these cases either ring closure did not take place, of if hydrogen sulfide were evolved, no phenothiazine could be isolated on working up the product. Many variations of the experimental conditions were attempted; time and temperature were altered, aluminum chloride was used as a catalyst, a solvent such as nitrobenzene was used, and in some cases the use of sulfur dichloride at room temperature in benzene instead of sulfur was attempted. None of these variations was successful, however. One attempt was made to cyclize bis(4-trifluoromethylphenyl)amine with thionyl chloride and aluminum chloride; a 50% yield of the unreacted amine was the only product recovered from this reaction.

It will be noted that in the case of the N-phenylnaphthylamines, the only successful ring closure was with N-(3-fluorophenyl)-2-naphthylamine (III). The structure of the product is uncertain, but is thought to be 8-fluoro-3,4-benzophenothiazine (IV) rather than 8-fluoro-2,3-benzophenothiazine (V) because the formation of (IV) involves condensation with the more active 1-position in naphthalene. The structure of substituted phenothiazines is most difficult to prove by degradation;



III

IV

V

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[2] Present addresses: J. A. Montgomery, Southern Research Institute, Birmingham, Alabama; W. A. Yarnall, 609 Sixth Avenue, Great Falls, Montana; V. A. Hoyle, Jr., Department of Chemistry, University of Texas, Austin, Texas.

[3] Smith, *J. Org. Chem.*, **15**, 1125 (1950).

[4] Smith, *J. Org. Chem.*, **16**, 415 (1951).

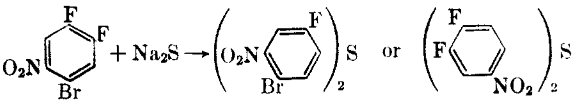
[5] Roe and Little, *J. Org. Chem.*, **20**, 1577 (1955).

[6] Bernsthen, *Ber.*, **16**, 2896 (1883).

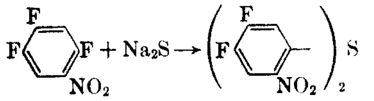
[7] Knoevenagel, *J. prakt. Chem.*, [2], **89**, 11 (1914).

most methods remove sulfur [hydrogen iodide cleavage,[8] catalytic reduction,[9] distillation from zinc dust[10]] forming the original diphenylamine, whereas the transformation of phenothiazines into carbazoles by heating with copper[10] is useless unless the structure of the resulting carbazole is known. The use of infrared spectra in determining structure of these compounds is discussed elsewhere.[3,5]

Another possible method for the preparation of phenothiazines analogous to a preparation of phenazines[11] is heating 2,2′-diaminodiphenyl sulfide with zinc chloride. This method was attempted without success with bis(2-amino-4-trifluorophenyl) sulfide. An interesting reaction was encountered in the attempted synthesis of 2,2′-diamino-4,4′,5,5′-tetrafluorodiphenyl sulfide for another attempted ring closure with zinc chloride. The synthesis was attempted by the reaction of 2-bromo-4,5-difluoronitrobenzene (VI) with sodium sulfide; it was mistakenly assumed that the bromine *ortho* to the nitro group would be more active than the fluorine *para* to it. The error in this assumption was discovered when the product was found to contain bromine, and analyzed correctly for compound VII. The reaction of 2,4,5-trifluoronitrobenzene (IX) with sodium sulfide gave a product giving the correct analysis for 2,2′-dinitro-4,4′,5,5′-tetrafluorodiphenyl sulfide (X). The structure assigned to X assumes that a fluorine *ortho* to a nitro group will be replaced more readily than a *para* fluorine; bolstering this assumption is the finding of Swarts[12] that 2,4-difluoronitrobenzene reacts with sodium methoxide to form 2-methoxy-4-fluoronitrobenzene, the structure of which was proved definitely by Hodgson and Nixon.[13] The diamine was made by reduction of X with iron powder and ammonium chloride, but an accident overtook the compound before structure proof could be completed.



VI VII VIII



IX X

EXPERIMENTAL

3,4-Difluoroacetanilide (I). 3,4-Difluoroaniline was produced in 80% yield from *o*-difluorobenzene by the method of VanderWerf[14]; acetylation with acetic anhydride and sodium acetate in water gave I in 90% yield, m.p. 125–126°. A 5% yield of I was obtained by the Schiemann reaction[15] starting with 3-amino-4-fluoroacetanilide; the literature indicated this was a difficult method.[14]

Anal. Calc'd for $C_8H_7F_2NO$: N, 8.19. Found: N, 8.18.

2-Fluoro-5-bromoaniline (II). 2-Fluoro-5-bromonitrobenzene[16] (355 g., 1.61 moles) was added dropwise to a stirred boiling solution of 60 g. of ammonium chloride in 1200 ml. of water, with 324 g. of iron filings suspended; the solution was refluxed 6 hours after addition was complete. The mixture then was steam-distilled, the distillate extracted with ether, the ether solution dried over magnesium sulfate, and the solvent removed. Distillation of the residue gave 202 g. (66%) of a colorless liquid, b.p. 91–92° at 9 mm.; n_D^{25} 1.5875.

Anal. Calc'd for C_6H_5BrFN: N, 7.37. Found: N, 7.53.

3,4-Difluorobromobenzene (III). *Method A.* This diazotization of 76 g. of II in fluoroboric acid in the usual manner[15] gave 97 g. (84%) of 2-fluoro-5-bromobenzenediazonium fluoborate; decomposition of this air-dried salt gave only 8% of IV, b.p. 151.5–152.5°; n_D^{25} 1.5036.

Method B. Bromination of 20 g. of refluxing *o*-difluorobenzene[14] in the presence of 1 g. of iron filings was carried out by adding 11.2 ml. of bromine during 1.5 hours, then continuing the refluxing for 2 hours. The mixture was steam-distilled, the distillate extracted with ether, dried over magnesium sulfate, and the solvent was removed; 20 g. (60%) of III was obtained, b.p. 150.5–151.5°; n_D^{25} 1.5038.

Anal. Calc'd for $C_6H_3BrF_2$: Br, 41.4. Found: Br, 41.5.

2-Bromo-4,5-difluoronitrobenzene (IV). Compound III (9.5 g., 0.049 mole) was added dropwise to a stirred mixture of 12 ml. of yellow fuming nitric acid and 50 ml. of conc'd sulfuric acid; the temperature was not allowed to go above 38°, and the solution was stirred 2 hours after the addition was complete. The reaction mixture then was poured on ice, extracted with ether, and the ether was washed with water, sodium bicarbonate solution, again with water, and finally dried over magnesium sulfate. Distillation of the product after removal of the ether gave 9.3 g. (80%) of IV, b.p. 72–74° at 4 mm. n_D^{20} 1.5484.

Anal. Calc'd for $C_6H_2BrF_2NO_2$: N, 5.87. Found: N, 5.66.

Preparation of the fluorodiphenylamines. All these compounds, shown in Table I, were prepared by the method of Goldberg[17] as modified slightly.[5]

3,7-Difluorophenothiazine (XVI). A mixture of 1 g. of 4,4′-difluorodiphenylamine,[18] 0.25 g. of sulfur, and a crystal of iodine was placed in a test tube and heated to 190–200° for 25 minutes (both the time and temperature in this preparation are critical); hydrogen sulfide was evolved. The mixture was cooled, dissolved in warm carbon tetrachloride, treated with Norit and zinc dust, filtered, and cooled. The yield of XVI, yellow plates, was 0.44 g. (39%), m.p. 165–167°.

Anal. Calc'd for $C_{12}H_7F_2NS$: C, 61.3; H, 2.98; N, 5.96. Found: C, 61.6; H, 3.07; N, 5.98.

2,7-Difluorophenothiazine (XVII). A mixture of 3.5 g. of 3,4′-difluorodiphenylamine (VII), 0.9 g. of sulfur, and a crystal of iodine was heated at 210–215° for 15 minutes under a nitrogen atmosphere; hydrogen sulfide was evolved. Recrystallization of the product from carbon tetrachloride after Norit treatment gave a product m.p. 120–130°; this impure product was washed with a solution of aqueous sodium sulfide twice to remove residual sulfur, and two

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(8) Baltzly, Harfenist, and Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(9) Shah, Tilak, and Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 142 (1948) [*Chem. Abstr.*, **44**, 3958 (1950)].

(10) Bernsthen, *Ann.*, **230**, 77 (1885).

(11) DuVal, *Anal. Chem. Acta*, **3**, 21 (1949) [*Chem. Abstr.*, **43**, 8299 (1949)].

(12) Swarts, *Rec. trav. chim.*, **35**, 154 (1915).

(13) Hodgson and Nixon, *J. Chem. Soc.*, 1879 (1928).

(14) Helin and VanderWerf, *J. Am. Chem. Soc.*, **73**, 5884 (1951).

(15) Roe, *Org. Reactions*, **5**, 193 (1949).

(16) Van Hove, *Bull. Acad. roy. Belg.*, [5] **12**, 804 (1927).

(17) Goldberg, *Ber.*, **40**, 4541 (1907).

(18) Leonard and Sutton, *J. Am. Chem. Soc.*, **70**, 1565 (1948).

TABLE I

PREPARATION AND PROPERTIES OF FLUORODIARYLAMINES

No.	Diphenylamine	Acetanilide Used	Bromobenzene Used	Yield, %	B.P., °C.	Mm.	M.P., °C.	Analyses, N Calc'd	Analyses, N Found
V	2,2′-Difluoro-	2-Fluoro-[c]	2-Fluoro[i]	6	120	5	<20	6.82	6.95
VI	3,3′-Difluoro-	3-Fluoro-[d]	3-Fluoro-[i]	51	138–140	6	<20	6.82	6.61, 6.72
VII	3,4′-Difluoro-	4-Fluoro-[c]	3-Fluoro-[i]	11	159	10	<20	6.82	6.71
VIII	3-Trifluoromethyl-4-fluoro-	3-Trifluoromethyl-[e]	4-Fluoro-[h]	49	127–128	6	<20	5.49	5.26, 5.41
IX	4,4′(bis)Trifluoromethyl-	4-Trifluoromethyl-[f]	4-Trifluoromethyl-[j]	67	133	4	55–57	4.59	4.83, 4.67
X	3,3′,4,4′-Tetrafluoro-	3,4-Difluoro-[b]	3,4-Difluoro-[b]	50	125-127	5	58–60	5.81	5.91
	Naphthylamine	Acetylaminonaphthalene Used							
XI	N-(3-Fluorophenyl)-1-	1-	3-Fluoro-[i]	72	180	2–3	<20	5.91	6.13
XII	N-(3-Fluorophenyl)-2-	2-	3-Fluoro-[i]	73	212–214	5–6	74–75	5.91	6.14, 6.09
XIII	N-(4-Fluorophenyl)-1-	1-	4-Fluoro-[h]	88	189	5–6	92–93	5.91	6.19, 5.95
XIV	N-(4-Fluorophenyl)-2-[a]	2-	4-Fluoro-[h]	85	189	3	86	—	—
XV	4-Fluoro-1-N-phenyl-	4-Fluoro-1-[g]	Bromobenzene	30	—		74–75	5.91	5.99

[a] Prepared by Smith, *J. Org. Chem.*, **16**, 415 (1951) from *p*-fluoroaniline and 2-naphthol. [b] See experimental part of this paper. [c] Holleman, *Rec. trav. chim.*, **25**, 330 (1906). [d] de Crauw, *Rec. trav. chim.*, **48**, 1061 (1929). [e] Swarts, *Bull. Acad. roy. Belg.*, (3), **35**, 375 (1898). [f] Jones, *J. Am. Chem. Soc.*, **69**, 2346 (1947). [g] Schiemann, Gueffroy, and Winkelmüller, *Ann.*, **487**, 270 (1931). [h] Schiemann and Pillarsky, *Ber.*, **64**, 1340 (1931). [i] Kharasch, *J. Org. Chem.*, **3**, 347 (1938). [j] Markarian, *J. Am. Chem. Soc.*, **74**, 1858 (1952).

further recrystallizations from carbon tetrachloride gave 0.25 g. of XVII, m.p. 153–155°.

Anal. Calc'd for $C_{12}H_7F_2NS$: C, 61.3; H, 2.98; N, 5.96. Found: C, 61.1; H, 2.94; N, 5.96, 5.98.

2,8-Difluorophenothiazine (XVIII). The best yield was obtained by heating 3.4 g. of 3,3′-difluorodiphenylamine (VI), 0.84 g. of sulfur, and several iodine crystals at 205–210° for 15 minutes under a nitrogen atmosphere; hydrogen sulfide was evolved. The crude product was dissolved in warm carbon tetrachloride, treated with zinc dust and Norit, and the solution was filtered and cooled. Two further recrystallizations from the same solvent gave a 50% yield of XVIII, light yellow crystals m.p. 198° (dec.).

Anal. Calc'd for $C_{12}H_7F_2NS$: C, 61.3, H, 2.98; N, 5.96. Found: C, 61.2; H, 3.05; N, 6.04.

8-Fluoro-3,4-benzophenothiazine (XIX). A mixture of 2 g. of N-(3-fluorophenyl)-2-naphthylamine (XII), 0.5 g. of sulfur, and an iodine crystal was heated to 175–185° until no more hydrogen sulfide was evolved; the product was worked up as described for XVIII, giving 1 g. of XIX as light green crystals, m.p. 159–160°. Several other runs made under slightly different conditions gave none of the desired product.

Anal. Calc'd for $C_{16}H_{10}FNS$: C, 71.9; H, 3.75; N, 5.24. Found: C, 72.3; H, 3.98; N, 5.24, 5.34.

Attempted preparation of other fluorophenothiazines. Pilot runs using both N-phenyl-1- and N-phenyl-2-naphthylamine using conditions described for XIX gave 80–90% yields of the expected benzophenothiazines. Repeated attempts to form a phenothiazine from XI, XIII, XIV, and XV using these conditions, and modifications thereof, failed. The same is true of other fluorodiphenylamines reported in this paper from which no phenothiazines were obtained—V, VIII, IX, and X.

Bis(2-Fluoro-4-nitro-5-bromophenyl) sulfide (XX). The reaction of 1.2 g. of 2-bromo-4,5-difluoronitrobenzene (IV) with sodium sulfide was carried out as described by Caldwell and Sayin[19] for similar compounds. The material obtained was sublimed *in vacuo*, then recrystallized from ethanol; a yield of 1 g. was obtained, m.p. 143–144°.

Anal. Calc'd for $C_{12}H_4Br_2F_2N_2O_4S$: Br, 34.0; N, 5.96. Found: Br, 34.3; N, 6.39, 6.21.

Bis(2-Nitro-4,5-difluorophenyl) sulfide (XXI). The reaction of 7.4 g. of 2,4,5-trifluoronitrobenzene[20] and 5 g. of sodium sulfide was carried out as for XX. After two sublimations *in vacuo* and recrystallization from methanol the product (3 g.) melted sharply at 109–111°.

Anal. Calc'd for $C_{12}H_4F_4N_2O_4S$: N, 8.04; S, 9.19. Found: N, 8.10; S, 9.31.

Bis(2-Amino-4,5-difluorophenyl) sulfide (XXII). A mixture of 2 g. of XXI, 2.5 g. of iron powder, and 2 g. of ammonium chloride was refluxed in 60 ml. of 60% ethanol for 3 days; 50 ml. more ethanol was added to the hot solution and the mixture was filtered and cooled. The precipitate which formed was again dissolved in hot ethanol, treated with Norit, filtered, and cooled; addition of water brought down a light pink precipitate, sublimation of which gave 0.9 g. of cream-colored crystals, m.p. 119–120°.

Anal. Calc'd for $C_{12}H_8F_4N_2S$: N, 9.72. Found: N, 9.98.

Disaster overtook this compound before further work could be done to prove its structure or to attempt ring closure with it.

Bis(2-Nitro-4-trifluoromethylphenyl) sulfide (XXIII). A solution of 19 g. (0.09 mole) of 3-nitro-4-chlorobenzotrifluoride[21] and 10.8 g. (0.045 mole) of sodium sulfide$\cdot 9H_2O$ in 60 ml. of ethanol was refluxed for 45 minutes, allowed to stand 2 hours, and the insoluble product was recrystallized twice from 95% ethanol giving 8.7 g. (90%) of XXIII, m.p. 142–143°.

Anal. Calc'd for $C_{14}H_6F_6N_2O_4S$: N, 6.80; S, 7.97. Found: N, 6.75; S, 8.01.

Bis(2-Amino-4-trifluoromethylphenyl) sulfide (XXIV). The reduction of 3 g. of XXIII was carried out as for XXII; sublimation *in vacuo* of the product gave 1.5 g. of XXIV, m.p. 89–90°.

Anal. Calc'd for $C_{14}H_{10}F_6N_2S$: N, 7.96; S, 9.09. Found: N, 7.61, 7.80; S, 9.31.

Several attempts to prepare 2,8-bis(trifluoromethyl)-phenothiazine from XXIV by heating with zinc chloride at

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(19) Caldwell and Sayin, *J. Am. Chem. Soc.*, **73**, 5125 (1951).

(20) Finger, *et al.*, *J. Am. Chem. Soc.*, **73**, 145 (1951).

(21) I. G. Farbenind. A. G., French Patent 745,293, May 8, 1933 [*Chem. Abstr.*, **27**, 4414 (1933)].

temperatures from 210° to 240° gave black tars from which none of the desired product could be isolated.

Attempted formation of phenothiazines from diphenylamines. Earlier in this article is a list of eight fluorodiphenylamines from which, after attempted thionation, no phenothiazine could be isolated. In the case of 4,4′-bis(trifluoromethyl)diphenylamine, little if any hydrogen sulfide was evolved upon heating with sulfur and iodine to 200°. An unsuccessful attempt was also made to cyclize this compound with thionyl chloride and aluminum chloride.

It is probable that 3,3′,4,4′-tetrafluorodiphenylamine can be thionated to form 2,3,7,8-tetrafluorophenothiazine, although the correct combination of time and temperature of thionation was not found in this work. Heating 1 g. of the diphenylamine with 0.25 g. of sulfur and a crystal of iodine at 200° for 25 minutes gave no reaction and the amine was recovered, whereas heating the mixture to 215° resulted in a violent reaction from which only a tar could be isolated. Numerous attempts to find a happy medium failed; the use of nitrobenzene as a solvent did not help. One unsuccessful attempt was made to cyclize this tetrafluorodiphenylamine with sulfur monochloride in benzene under conditions which produced a good yield of unsubstituted phenothiazine from diphenylamine itself.

The other six fluorodiphenylamines listed reacted with sulfur and iodine to form hydrogen sulfide, but no phenothiazine was isolated. Here again, many variations of temperature and time of heating did not help.

CHAPEL HILL, N. C.