[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

THE PREPARATION OF SOME FLUORO- AND TRIFLUOROMETHYLPHENOTHIAZINES, AND SOME OBSERVATIONS REGARDING DETERMINATION OF THEIR STRUCTURE BY INFRARED SPECTROSCOPY[1]

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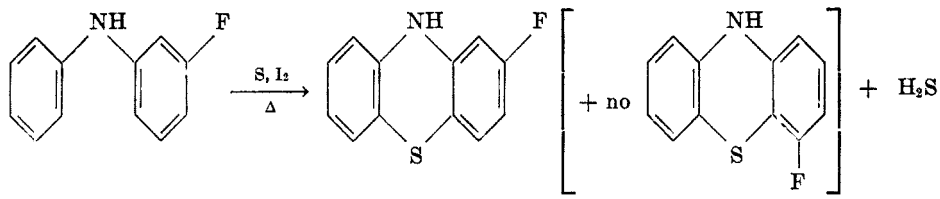
The preparation of fluorine-containing phenothiazines was of interest from several points of view, including evaluation of their use as antioxidants in lubricating oils of the type used in turbo-jet engines (I); this paper describes the preparation of several new fluorophenothiazines. Six were prepared by the action of sulfur on substituted diphenylamines (2, 3); these six are 1-fluoro-, 2-fluoro-, 2,4-difluoro-, 2,4,7-, and 2,4,8-trifluoro-, and 2,4,6,8-tetrafluorophenothiazine. Another, 2-trifluoromethylphenothiazine, was prepared by a Smiles rearrangement (4–6); this method was also used to make 3-fluoro- and 3-trifluoromethyl-phenothiazine, which had been previously prepared by Smith (7, 8) from the fluorodiphenylamines. In addition, the attempted preparation of several other fluorophenothiazines by both methods is reported. The infrared spectra of these and other fluorophenothiazines prepared in this laboratory (9) were obtained, and some conclusions were reached regarding the use of infrared spectra in assigning structure to fluorophenothiazines.



I II III

Prior to this work, the only monofluorophenothiazine known was the 3-fluoro isomer (8). Two additional members of this series, 1- and 2-fluorophenothiazine, were prepared by thionation of 2- and 3-fluorodiphenylamine, respectively. Only one fluorophenothiazine was isolated from the reaction of sulfur with 3-fluorodiphenylamine (I), although two might be expected in view of the preparation by Charpentier (10) of both 2- and 4-chlorophenothiazine from 3-chlorodiphenylamine, and 2- and 4-methylphenothiazine from 3-methyldiphenylamine. (The 2-methylphenothiazine was formed in much greater yield than the 4- isomer; structures were proved by conversion (by heating with copper) to the corresponding methylcarbazoles. The chlorophenothiazine formed in greater amount from 3-chlorodiphenylamine was called the 2-isomer by analogy.) The single fluorophenothiazine obtained from 3-fluorodiphenylamine was tentatively

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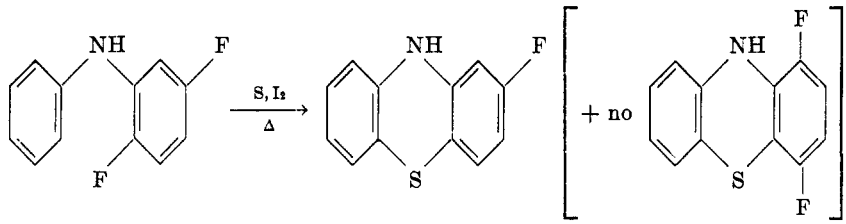
called the 2- isomer by analogy with Charpentier's work, because of the known predominance of *para* over *ortho* orientation of incoming groups by fluorine (11), and because of infrared evidence discussed below. Later, this structure was confirmed unexpectedly during an attempt to prepare 1,4-difluorophenothiazine (VI) by thionation of 2,5-difluorodiphenylamine (IV) in a sealed tube reaction. A small amount of product was isolated which turned out to be a monofluorophenothiazine; it proved by analysis, melting point, and infrared spectrum to be identical with the compound obtained from the ring closure of 3-fluorodiphenylamine, and is in all probability the 2-isomer (V), as the formation of 4-fluorophenothiazine from IV under these conditions is unlikely. An unsuccessful attempt to prepare V by the Smiles rearrangement is discussed below.



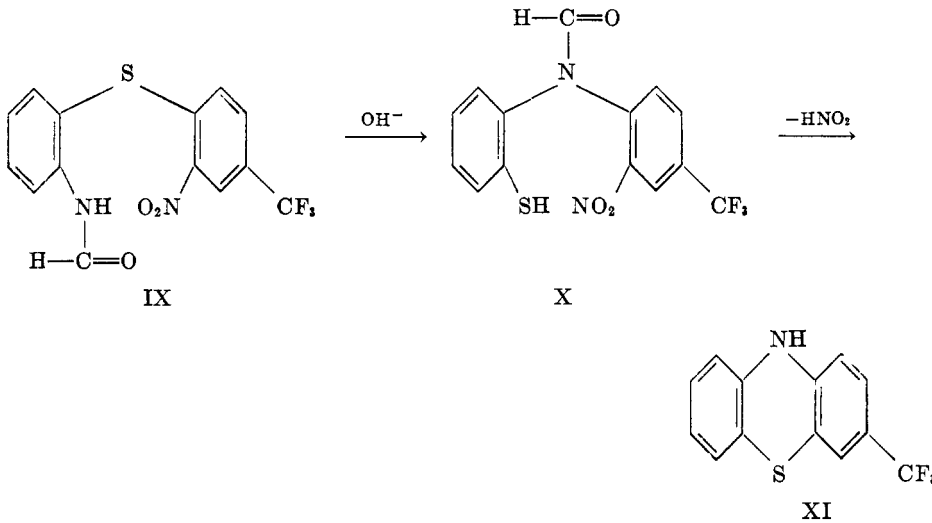
IV V VI

With the loss of fluorine during thionation of IV in mind, a careful study was made of the product obtained by thionation of 2-fluorodiphenylamine (VII). Although the yields were low, reaction at 200–210° gave a 9.3% yield of 1-fluorophenothiazine (VIII) and a 1.4% yield of phenothiazine itself; in a sealed tube at 325°, unsubstituted phenothiazine was obtained in 16% yield, with a much smaller yield of VIII. To see if this replacement of halogen by sulfur in ring closure would be of synthetic value, one attempt was made to prepare VIII by sealed-tube thionation of 2-chloro-6-fluorodiphenylamine; however, no product could be isolated from the tarry reaction product.

Many attempts were made to prepare 1,4-difluorophenothiazine (VI) from IV; a red viscous tar was the usual product. It is interesting to note that similar tars were obtained in efforts to prepare 1,3-difluoro-, 1,4,7-trifluoro-, and 1,4,8-trifluorophenothiazine as well as 1,8-difluorophenothiazine (9) from the appropriate diphenylamines. In all these syntheses, hydrogen sulfide was evolved, but intractible tars resulted. Common to all these diphenylamines is a fluorine in the 2- position; it is not clear why this should cause difficulty. The fact that a successful synthesis of two trifluorophenothiazines and a tetrafluorophenothiazine was accomplished indicates that the position of the fluorine atoms present rather than their number affects the ring closure.

Several other methods of preparing phenothiazines are reported in the literature (12), but the only other one of practical interest at present involves the Smiles rearrangement of a 2-amido-2′-nitrodiphenyl sulfide (4–6, 12) followed by ring closure by loss of nitrous acid. The rearrangement involves a nucleophilic replacement of the sulfur on the nitro-bearing ring by nitrogen of the

amide function, and is illustrated by the formation of 3-trifluoromethylphenothiazine (XI) from 2-nitro-2′-formamido-4-trifluoromethyldiphenyl sulfide (IX) in 52% yield. It was found that the formamido compounds gave much better yields and cleaner products than the benzoyl derivatives used by Smiles; this is in part due to difficulties in isolating the product in the presence of the ethyl benzoate formed during the reaction. In all cases using the formamido derivative, the free phenothiazine rather than the acylated product was isolated.



IX X XI

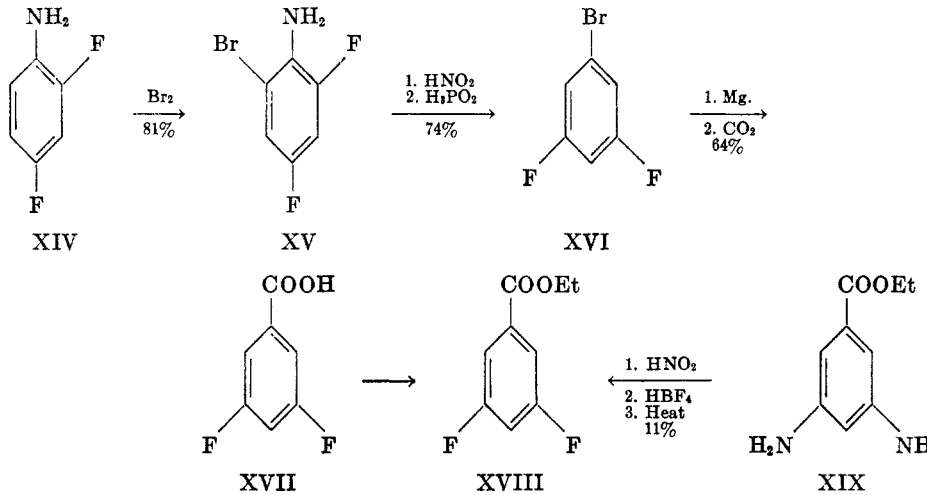
The preparation of 2-trifluoromethylphenothiazine from 2-nitro-2′-formamido-5-trifluoromethyldiphenyl sulfide in 59% yield confirmed the structure assigned this compound by Smith (7), who prepared it by thionation of 3-trifluoromethyldiphenylamine. 3-Fluorophenothiazine was prepared from 2-nitro-2′-formamido-4-fluorodiphenyl sulfide in 43% yield; this compound had previously been prepared by Smith (8) from 4-fluorodiphenylamine.

An attempted preparation of 2-fluorophenothiazine from 2-nitro-2′-formamido-5-fluorodiphenyl sulfide (XII) was unsuccessful; such a synthesis, if successful, would have been further confirmation of the structure of this compound, discussed above. The reaction product was an orange powder, m.p. 160–170°, containing sulfur and about 7% nitrogen, but no fluorine. It resisted all attempts at purification, and it was not further characterized. Because of the failure of this synthesis, no attempt was made to prepare 4-fluorophenothiazine by this method from 2-nitro-2′-formamido-3-fluorodiphenyl sulfide. Here the fluorine is *ortho* to the nitro group, and would be expected to be lost much more easily than the *para*-fluorine in XII (13).

Unsuccessful attempts were made to prepare 4-trifluoromethylphenothiazine from 2-nitro-2′-formamido-3-trifluoromethyldiphenyl sulfide; this sulfide was resistant to rearrangement, an almost quantitative recovery of it being made

in one experiment under conditions which formed phenothiazines in other cases. Increasing the reflux time from 0.5 hour to 1.5 hours, and using an excess of sodium hydroxide did result in the formation of a small amount of a phenothiazine, (as indicated by the red color produced with nitric acid, and the formation of sodium nitrite), but no pure product was isolated.

The preparation of most of the intermediates needed for making the new fluorodiphenylamines and fluorodiphenyl sulfides here reported was routine, but several points in the synthesis of 3,5-difluorobenzoic acid and 3,5-difluorobromobenzene might be of interest. An improved synthesis of *m*-difluorobenzene in 65% yield from *m*-phenylenediamine was developed using the bis-diazonium fluoborate prepared in 40% fluoboric acid; this doubles previously reported yields (13A, 13B). This method did not work for *p*-difluorobenzene, which was best made by literature methods (13A, 13B).



Bromination of 2,4-difluoroaniline (XIV) in glacial acetic acid produced 2,4-difluoro-6-bromoaniline (XV); it was found that 2,4-difluoroacetanilide resisted bromination in refluxing glacial acetic acid and gave no acetyl-XV. De-amination of XV produced 3,5-difluorobromobenzene (XVI) which was transformed by a Grignard reaction to 3,5-difluorobenzoic acid (XVII); the yield of XVII from XIV was about 40%, and the ethyl ester (XVIII) was prepared in good yield. XVIII was also prepared in 11% yield from ethyl 3, 5-diaminobenzoate (XIX) via the bis-diazonium fluoborate.

Determination of the structure of a phenothiazine by degradation is difficult; the methods used form a diphenylamine by removal of sulfur (14–16), or convert the molecule to a carbazole (10, 17) or to an acridine (18). Formation of the diphenylamine does not distinguish between 2- and 4-phenothiazines, and the conditions for transformation to carbazoles and acridines are not gentle; in addition, the structure of these derivatives must be known. Because of the difficulty of these methods of structure proof, a reliable method involving infrared spectra would be most useful.

Thompson and co-workers (19, 20), and Barnes (21) showed that for substituted benzene rings, the peak at 14.9 microns (assigned to the vibration of the carbon ring as a unit perpendicular to the plane of the hydrogen atoms) shifts more as a function of the relative positions then the nature of substituents. The data are summarized below:

Type of Substitution	*Location of the Absorption Peak (Microns)*
mono-substitution	13.2–13.5
o-di-substitution	13.3–13.5
m-di-substitution	12.7–13.0
p-di-substitution	12.0–12.3
vic-tri-substitution	13.0–13.2
asymm-tri-substitution	12.3–12.5
sym-tri-substitution	12.0–12.1

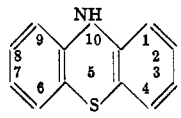
Since 2-trifluoromethylphenothiazine contains an *asymmetrically* trisubstituted benzene ring and 4-trifluoromethylphenothiazine has a *vicinal* structure, the two compounds should be distinguishable from their infrared spectra. Smith (7) showed that the product of the ring closure of 3-trifluoromethyldiphenylamine with sulfur had an absorption peak at 12.17 μ, and on this basis called it 2-trifluoromethylphenothiazine.

Since the phenothiazine structure is composed of two benzene rings joined in the *ortho* positions, it would be expected that each ring should exhibit infrared absorption characteristic of the type of substitution found in that ring. For example, phenothiazine substituted in the 1-position should exhibit two absorption peaks, one in the region assigned to *vicinal* trisubstitution (due to the substituent in the 1-position and the adjacent nitrogen and sulfur bridges of the phenothiazine structure) and one peak in the region for *ortho*-disubstitution (for the *ortho* nitrogen and sulfur bridges). When the two rings are identical, as in the case of phenothiazine itself and of 3,7-difluorophenothiazine, two peaks very close together and in the proper region might be expected.[2] In Table I are listed the absorption peaks in the region under consideration for various fluorophenothiazines containing *ortho* disubstituted, *vicinal* trisubstituted, and *asymmetric* trisubstituted rings. Phenothiazine itself has two peaks at 13.3 and 13.6 μ, both within the region for *o*-disubstitution, and no other peak between 12.0 and 13.5 μ. 1-Fluorophenothiazine has two peaks, one at 13.0 μ for the *vicinal* trisubstituted structure and one at 13.4 μ for the other ring, which is *o*-disubstituted. The other monosubstituted phenothiazines in the Table are all composed of one *o*-disubstituted ring and one *asymmetrically* trisubstituted ring. In each case two peaks are found in the infrared corresponding to these two types of substitution, with no extraneous peaks in the region. 3,7-Difluoro- and 2,7-difluoro-phenothiazine each have two peaks in the region for *asymmetric* trisubstitution as predicted, but in addition there are also peaks in the region for *o*-disubstitution, though these two compounds do not contain this structure. This raises some question about the assignment of these peaks to *o*-disubstitution. 2,4-Difluorophenothiazine absorbs in the region for disubstitution, as it

[2] Professor Joseph W. Straley, private communication.

TABLE I

INFRARED SPECTRA OF FLUORO- AND TRIFLUOROMETHYL-PHENOTHIAZINES BETWEEN 12.0 AND 13.5 MICRONS

	12.3–12.5 μ (*asymm.*)	13.0–13.2 μ (*vic.*)	13.3–13.5 μ (*o*-disubs.)	Other Peaks
1. Phenothiazine	—	—	13.3, 13.6	—
2. 1-Fluoro-	—	13.0	13.4	—
3. 2-Fluoro-	12.55	—	13.5	—
4. 3-Fluoro-	12.4	—	13.5	—
5. 2-Trifluoromethyl-	12.2	—	13.3	—
6. 3-Trifluoromethyl-	12.1	—	13.3	—
7. 3,7-Difluoro-[b]	12.1, 12.2	—	(13.4)[a]	—
8. 2,7-Difluoro-[b]	12.3, 12.5	—	(13.3)[a]	12.85 (w)
9. 2,4,8-Trifluoro-	12.5	—	—	12.2
10. 2,4,7-Trifluoro-	12.5	—	—	12.1, 12.2 (w)
11. 2,4-Difluoro-	(12.4)[a]	—	13.3, 13.5	12.1
12. 2,4,6,8-Tetrafluoro-	(12.6)[a]	—	—	12.0, 12.1

[a] Structure corresponding to this bond not present in molecule.

[b] Reference no. 9.

should. The compounds 9–12 have substituents on both rings and do not absorb in the region assigned for *o*-disubstitution.

Discrepancies in the region between 12.3 and 12.5 μ for *asymmetric* trisubstitution are found with 2,4-difluoro- and 2,4,6,8-tetrafluoro-phenothiazine, but it should be pointed out that all the compounds numbered 9–12 contain at least one tetrasubstituted benzene ring, a case where no assignment has been made. It is interesting to note that all the structures containing 1,2,3,5-tetrasubstitution absorb between 12.0 and 12.2 μ, and that two of them (numbers 11 and 12), have bands corresponding to *asymmetric* substitution, but do not have that structure.

To summarize the infrared evidence, it was found that each compound did have the predicted infrared absorption peak for its structure, but in many cases additional peaks were found corresponding to substituted benzene structures not contained in the molecules. Therefore, it is concluded that application of infrared analysis to structure determination in the phenothiazine series should be approached with caution.

EXPERIMENTAL

All melting points are corrected.

2,4-Difluoro-6-bromoaniline (I). A solution of 16 g. (0.10 mole) of bromine in 25 ml. of acetic acid was added slowly with stirring to a solution of 12.9 g. (0.10 mole) of 2,4-difluoroaniline (13) in 75 ml. of glacial acetic acid. Intermittent cooling with an ice-bath kept the reaction mixture at about 25°. One half-hour after all the bromine had been added, the slight bromine color remaining was removed with a small amount of sodium thiosulfate solution; a solution of 11.2 g. of sodium acetate in 100 ml. of water was added, and the

mixture was cooled in an ice-bath to complete precipitation. The yield was 17 g. (81%) of I, m.p. 41–42° (from 50% ethanol). I has a high vapor pressure; a sample left overnight to dry had disappeared completely by morning.

Anal. Calc'd for $C_6H_4BrF_2N$: N, 6.73. Found: N, 6.71.

2,4-Difluoro-6-bromoacetanilide (II). Acetylation of I in acetic anhydride, and recrystallation of the product from alcohol and water after Norit treatment, gave a 90% yield of II, m.p. 156–157°.

Anal. Calc'd for $C_8H_6BrF_2NO$: N, 5.60. Found: N, 5.53.

Attempts to acetylate the amine by the aqueous method with acetic anhydride failed, due to the slight solubility of the amine in dilute hydrochloric acid.

2,4-Difluoroacetanilide resisted bromination in refluxing acetic acid to give II.

3,5-Difluorobromobenzene (III). The de-amination of 16 g. of I was carried out with hypophosphorous acid according to the directions of Kornblum (22). A yield of 11 g. (74%) of III was obtained; b.p. 140°; d^{28} 1.676, n_D^{23} 1.4989.

Anal. Calc'd for $C_6H_3BrF_2$: C, 37.34; H, 1.56.

Found: C, 37.25; H, 1.58.

3,5-Difluorobenzoic acid (IV). *Method A*. A 250-ml. 3-neck flask equipped with a stirrer, reflux condenser with a drying tube, and an addition funnel contained 1.9 g. (0.075 m.) of magnesium ribbon and 50 ml. of dry ether; several drops of methyl iodide was added to the mixture, then 14.5 g. (0.075 m.) of III was added dropwise. The Grignard solution was added to a slurry of Dry Ice in ether, and the acid was isolated in the usual manner; it was purified by sublimation at 90° and 10 mm., yielding 7 g. (64%) of IV, m.p. 121–122°.

Anal. Calc'd for $C_7H_4F_2O_2$: C, 53.17; H, 2.56; Neut. equiv., 158.1.

Found: C, 53.13; H, 2.89; Neut. equiv., 158.5.

Method B. A solution of 18 g. (0.10 mole) of ethyl 3,5-diaminobenzoate (23) in 480 g. of 45% fluoboric acid was cooled to −10°, and 15 g. (0.22 mole) of sodium nitrite was added in small portions with stirring. After addition was complete, the *bis*-diazonium fluoborate was filtered and washed with three portions of cold ether and dried; 40 g. of salt was obtained—somewhat more than theoretical—presumably due to co-precipitation of sodium fluoborate. The fluffy white salt decomposed at about 175°.

The decomposition of the *bis*-diazonium fluoborate was carried out in the usual way (24). The yield was very poor, and various diluents, such as sodium fluoride, sand, and others were tried to improve the yield. The best yield was obtained by decomposing the salt under diminished pressure (around 30 mm.) by attaching an aspirator to the exit of the trap system. The crude ester was saponified with potassium hydroxide solution, and IV was isolated in the usual way. The product melted at 121–122°, and a mixture melting point with a sample made by Method *A* showed no depression.

The *ethyl ester* was isolated by extracting an ether solution of the decomposition product of the *bis*-diazonium salt with aqueous sodium carbonate, washing with water, and drying with calcium sulfate. After removing the ether, the ester was distilled at 103–105° at 46 mm. *Ethyl 3,5-difluorobenzoate* is a colorless liquid with a sweet odor, b.p. 200° at 760 mm.; d^{26} 1.201; n_D^{25} 1.4670.

Anal. Calc'd for $C_9H_8F_2O_2$: C, 58.1; H, 4.33. Found: C, 58.4; H, 4.38.

2-Chloro-6-fluoroaniline (V). A solution of 23 g. (0.13 mole) of 2-chloro-6-fluorobenzoic acid (25) in 100 ml. of conc'd sulfuric acid was prepared by stirring at 60° for one hour, then 10 g. (0.15 mole) of sodium azide was added in small portions to the solution at 65° over a period of 1.5 hours. The mixture was allowed to stand overnight, after which period it was made basic with ammonium hydroxide and steam-distilled. The product was extracted from the steam-distillate with ether and dried over magnesium sulfate. Distillation yielded 13.5 g. (70%) of V, b.p. 91° at 30 mm.; d^{28} 1.316; n_D^{23} 1.5511.

Anal. Calc'd for C_6H_5ClFN: N, 9.62. Found: N, 9.55.

The *acetyl derivative* of this amine was prepared by refluxing 6 g. of V in 25 ml. of acetic acid containing 4.2 g. of acetic anhydride for 1.5 hours; 5.5 g. (71%) of 2-chloro-6-fluoroacetanilide was obtained as white platelets, m.p. 134–135° (from water).

Anal. Calc'd for C_8H_7ClFNO: N, 7.47. Found: N, 7.33.

2-Nitro-3-chlorobenzotrifluoride (VI). A solution of 24 g. (0.116 mole) of 2-nitro-3-aminobenzotrifluoride (26) in 300 ml. of hot 50% sulfuric acid was prepared, and the solution was cooled to 0°. To the stirred slurry was added 9.1 g. (0.13 mole) of sodium nitrite in small portions; the solution was stirred for 15 minutes after the addition was complete. The solution of diazonium salt was poured into 160 ml. of 10% cuprous chloride solution at 20°; the mixture was allowed to stand at room temperature for an hour while nitrogen was evolved, then was diluted with 100 ml. of water and the mixture was steam-distilled. The distillate was extracted with ether, dried with calcium chloride, the ether removed, and the product distilled under reduced pressure. A 52% yield of VI, b.p. 125–126° at 27 mm. was obtained; d^{24} 1.531; n_D^{24} 1.4782.

Anal. Calc'd for $C_7H_3ClF_3NO_2$: N, 6.21. Found: N, 6.34.

4-Nitro-3-chlorobenzotrifluoride (VII). A 53% yield of VII was obtained by the same method used for VI; b.p. 116° at 28 mm.; d^{24} 1.527; n_D^{24} 1.4864.

Anal. Calc'd for $C_7H_3ClF_3NO_2$: N, 6.21. Found: N, 6.15.

A mixture of VI and VII has been prepared by the nitration of *m*-chlorobenzotrifluoride (27, 28); the isomers were not separated or characterized, however.

Preparation of the fluorodiphenylamines. All the diphenylamines were prepared by a modification of the method of Goldberg (29) from the appropriately substituted acetanilides and bromobenzenes; Table II summarizes this information. In most cases, 0.1 mole of the acetanilide, 0.20 mole of the bromobenzene, 0.10 mole of anhydrous potassium carbonate, 20 ml. of nitrobenzene and 6.0 g. of the catalyst mixture (consisting of equal parts by weight of cuprous iodide, potassium iodide, and copper powder), were placed in a 250 ml. three-neck flask equipped with a reflux condenser and a stirrer. A crystal of iodine was added, and the system was brought to reflux and allowed to continue refluxing for 17 hours with vigorous stirring. At the end of the reflux period the nitrobenzene solvent and the excess bromobenzene were removed by steam-distillation and the acetyldiphenylamine was extracted with several portions of ether. The cold ether solution was treated with Norit, the ether was removed, and the residue was dissolved in 100 ml. of 20% alcoholic potassium hydroxide solution and refluxed for 3.5 hours. The hydrolysis mixture was poured into 800 ml. of saturated salt solution, extracted with several portions of ether, and the ether extract was dried with magnesium sulfate, the ether removed, and the residue distilled under diminished pressure. An early fraction of the unreacted aniline was sometimes recovered but the boiling points of the diphenylamines and the anilines were sufficiently far apart so that a good separation was obtained. The yields in Table II were calculated at this point, and the products were sufficiently pure for most purposes. Omission of the nitrobenzene in 2 cases led to lowered yields. For analysis, the diphenylamines were further purified by dissolving in ether and extracting twice with 1 *N* hydrochloric acid, once with 10% sodium hydroxide, and twice with water, followed by redistillation. Those which were solid then were recrystallized from 30–60° petroleum ether.

All of the fluorodiphenylamines gave color reactions with conc'd nitric acid on a spot plate. The diphenylamine (identified by the number as shown in Table II) and the colors given are: purple: VIII, IX, X, XI, XII, XVIII; brown: XIII, XIV, XV; orange: XVI; yellow: XVII.

The N-benzoyl derivative of 2-fluorodiphenylamine was made by refluxing a small amount of the diphenylamine with a slight excess of benzoyl chloride in benzene for 3 hours. Recrystallization from 50% ethanol, after Norit treatment, gave a product m.p. 129–130°.

Anal. Calc'd for $C_{19}H_{14}FNO$: N, 4.81. Found: N, 4.74.

Preparation of substituted diphenyl sulfides. The general procedure used was that of Bost, Turner, and Norton (30). A solution of the sodium salt of *o*-aminothiophenol was prepared by adding a solution of 4.0 g. (0.01 note) of sodium hydroxide in 30 ml. of water to a solution of 12.5 g. (0.10 mole) of *o*-aminothiophenol in 300 ml. of absolute ethanol. This solution then was added to a solution of 0.1 mole of the halonitrobenzene in 100 ml. of absolute ethanol; usually the reaction proceeded immediately with the precipitation of sodium chloride (or

TABLE II

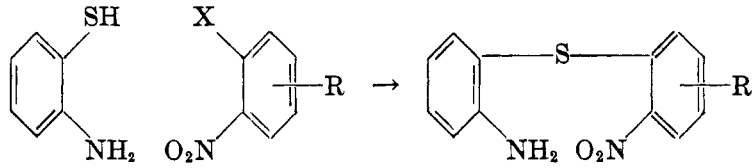
PREPARATION AND PROPERTIES OF THE FLUORODIPHENYLAMINES

	Diphenylamine	Acetanilide Used	Bromobenzene Used	M.P., °C.	B.P., °C.	mm.	Yield, %	Nitrogen	
								Calc'd	Found
VIII	2-Fluoro-	2-Fluoro-[f]	Bromobenzene	[a]	111.5	3	80	7.48	7.54
IX	3-Fluoro-	3-Fluoro-[g]	Bromobenzene	[b]	149–150	10	56[c]	7.48	7.52
IX	3-Fluoro-	Acetanilide	3-Fluoro-[l]				39		
X	2,5-Difluoro-	2,5-Difluoro-[k]	Bromobenzene	45–45.5	138	9	68	6.83	6.79
XI	2,4-Difluoro-	2,4-Difluoro-[i]	Bromobenzene	42–42.5	110–113	3	63	6.83	6.89
XII	3,5-Difluoro-	Acetanilide	3,5-Difluoro-[k]	45–45.5	121–124	4	51	8.83	6.70
XIII	2,3′,5-Trifluoro-	2,5-Difluoro-[k]	3-Fluoro-[l]	31.5–32	105–106	2.5	63	6.28	6.33
XIV	2,4′,5-Trifluoro-	2,5-Difluoro-[k]	4-Fluoro-[m]	39.2–40	104–105	2.5	71	6.28	6.18
XV	3,3′,5-Trifluoro-	3-Fluoro-[g]	3,5-Difluoro-[k]	27.5–28.5	121	3.5	49[d]	6.28	6.23
XVI	3,4′,5-Trifluoro-	4-Fluoro-[f]	3,5-Difluoro-[k]	60–61	127–128	4	65	6.28	6.16
XVII	3,3′,5,5′-Tetrafluoro-	3,5-Difluoro-[i]	3,5-Difluoro-[k]	117–118	[e]		43	5.81	5.82
XVIII	2-Chloro-6-fluoro-	2-Chloro-6-fluoro-[k]	Bromobenzene	69–69.3	138–140	4	34	6.32	6.25

[a] Yellow oil, d^{23} 1.165; n_D^{23} 1.6171. [b] Yellow oil, d^{23} 1.176; n_D^{23} 1.6203. [c] 71% based on recovered *m*-fluoroaniline. [d] 62% based on recovered *m*-fluoroaniline. [e] Not distilled. After removal of the ether the solid was recrystallized from 60–90° petroleum ether. [f] Holleman, *Rec. trav. chim.*, **25**, 330 (1906). [g] de Crauw, *Rec. trav. chim.*, **48**, 1061 (1929). [h] Swarts, *Rec. trav. chim.*, **33**, 299 (1914). [i] Ingold, *et al.*, *J. Chem. Soc.*, 971 (1936). [j] Finger, Reid, and Finnerty, *J. Am. Chem. Soc.*, **73**, 153 (1951). [k] See experimental section of this paper. [l] Kharasch, *J. Org. Chem.*, **3**, 347 (1938). [m] Schiemann and Pillarsky, *Ber.*, **64**, 1340 (1931).

TABLE III

SUBSTITUTED DIPHENYL SULFIDES



Diphenyl Sulfide R	Nitro Cpd. Used in Preparation X	Nitro Cpd. Used in Preparation R	Color	M.P., °C.	Yield, %	Analyses Calc'd C	Calc'd H	Found C	Found H
XIX 3-CF_3	2-Cl	6-CF_3[a]	Yellow	72–73	67	49.68	2.89	49.53	2.93
XX 4-CF_3	2-Cl	5-CF_3[b]	Yellow	108–109	89	49.68	2.89	49.52	2.88
XXI 5-CF_3	2-Cl	4-CF_3[c]	Yellow	110–111	80	49.68	2.89	49.70	2.90
XXII 4-F	2-F	5-F[d]	Red	73–74	70	54.54	3.43	54.48	3.38
XXIII 5-F	2-F	4-F[e]	Yellow	115–116.5	54	54.54	3.43	54.68	3.60

[a] Compound VI, this paper. [b]Obtained from Hooker Electrochemical Co. [c]Compound VII, this paper. [d]Swarts, *Rec. trav. chim.*, **33**, 299 (1914). [e]Swarts, *Rec. trav. chim.*, **35**, 154 (1915).

sodium fluoride when a fluoronitrobenzene was used). The mixture was brought to reflux for half an hour to insure completion of the reaction; this half-hour reflux period was sufficient in all cases except in the preparation of 2-nitro-2′-amino-3-trifluoromethyldiphenyl sulfide (XIX). This preparation required a reflux period of 3.5 hours, presumably due to the steric effect of the trifluoromethyl and chloro groups *ortho* to the nitro group.

At the end of the reflux period, the mixture was filtered from the precipitated sodium halide and was heated to boiling. Water (100 ml.) was added and the solution was allowed to cool to room temperature, then the solution was cooled more strongly. More rapid cooling resulted in oiling out of the product; in some cases this occurred anyway. The products all eventually precipitated as nicely crystalline compounds, which were further purified by recrystallation from 80% ethanol. Table III contains data on the substituted diphenyl sulfides prepared.

Preparation of N-formamido derivatives of the diphenyl sulfides. The N-formamido derivative of each substituted diphenyl sulfide was prepared by refluxing the diphenyl sulfide in 10 times its weight of 90% formic acid for 9 to 10 hours; after this time the reaction mixture was poured over ice and the formamido derivative came out of solution first as an oil, but solidified on standing. The products were purified by recrystallization from 75% ethanol after treatment with Norit. Table IV gives the details of these syntheses.

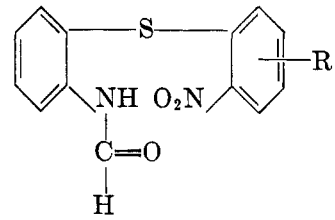
2-Nitro-2′-benzamido-4-trifluoromethyldiphenyl sulfide (XXIV). A mixture of 6.3 g. (0.02 mole) of 2-nitro-2′-amino-4-trifluoromethyldiphenyl sulfide (XX), 25 ml. of pyridine and 2.8 g. of benzoyl chloride was refluxed for an hour; the reaction mixture was poured over ice and the benzoyl derivative separated first as an oil, then solidified. Two recrystallizations from ethanol yielded 7.5 g. (89%) of the product, m.p. 127.5–128°.

Anal. Calc'd for $C_{20}H_{13}F_3N_2O_3S$: N, 6.69. Found: N, 6.73.

1-Fluorophenothiazine (XXX). *Method A.* A mixture of 15 g. (0.08 mole) of 2-fluorodiphenylamine (VIII), 5 g. (0.16 mole) of sulfur, and a few crystals of iodine was heated at 200–210° for three hours in a 50-ml. flask with reflux condenser; the reaction was accompanied by the evolution of hydrogen sulfide. The resulting dark colored tar was boiled with 20% aqueous sodium sulfide to remove unreacted sulfur. The residue, taken up with ether, was treated with Norit and zinc dust, filtered, and dried over magnesium sulfate, the ether

TABLE IV

N-FORMYL DERIVATIVES OF SUBSTITUTED DIPHENYL SULFIDES



Diphenyl Sulfide R		Color	M.P., °C.	Yield, %	Analyses			
					Calc'd		Found	
					C	H	C	H
XXV	3-CF_3	White	137–138	92	49.12	2.65	49.15	2.61
XXVI	4-CF_3	Yellow	132–133	88	49.12	2.65	49.16	2.77
XXVII	5-CF_3	Yellow	95–96	83	49.12	2.65	49.25	2.92
XXVIII	4-F	Yellow	128–129	74	53.42	3.10	53.63	3.17
XXIX	5-F	Yellow	116–117	74	53.42	3.10	53.50	3.24

was removed, and the residue distilled; 2.2 g. of VIII was recovered, and 3.0 g. of a yellow solid distilled at 140° at 2.5 mm., leaving a tarry residue in the flask. The solid distillate was dissolved in hot 30–60° petroleum ether, treated with Norit, and cooled in an ice-salt bath; it crystallized as a white solid. Fractional crystallization of this material from petroleum ether gave both XXX and unsubstituted phenothiazine. Separation was conveniently effected by allowing the hot solution to cool slowly to room temperature; phenothiazine precipitated at this temperature, while the more soluble XXX crystallized on stronger cooling of the filtrate in an ice-salt bath. The phenothiazine (0.2 g.) melted at 180–182°, and was identified by a mixture melting point with an authentic sample and by infrared analysis. The yield of XXX was 1.7 g., m.p. 81.5–82° (after sublimation at 125° and 2 mm., followed by recrystallization from petroleum ether.) Based on the recovered diphenylamine, the yields of phenothiazine and XXX were 1.4% and 9.3% respectively.

Anal. Calc'd for $C_{12}H_8FNS$: C, 66.3; H, 3.71; N, 6.45.
Found: C, 66.4, 66.5; H, 3.84, 3.75; N, 6.45.

XXX gives a blood red color with conc'd nitric acid.

Method B. A mixture of 1.9 g. of VIII, 0.6 g. of sulfur, and a crystal of iodine was heated in a sealed tube at 310 to 340° for 1.5 hours. Working up the mixture as described in Method *A* gave a few milligrams of XXX, plus 0.175 g. of phenothiazine.

Method C. This method was unsuccessful; 2.2 g. of 2-chloro-6-fluorodiphenylamine (XVIII), 0.6 g. of sulfur, and a crystal of iodine were heated in a sealed tube at 300° for 1.5 hours; no crystalline product could be isolated from this reaction.

2-Fluorophenothiazine (XXXI). *Method A.* A mixture of 5.0 g. (0.027 mole) of 3-fluorodiphenylamine (IX), 1.7 g. (0.53 mole) of sulfur, and a few crystals of iodine was heated in a test tube at 180 ± 5° for one hour. On cooling, the entire mass solidified and was extracted with hot carbon tetrachloride; the extract was treated with Norit and zinc dust, and filtered. The crude XXXI was crystallized from the filtrate in an ice-salt bath, and then was boiled with 20% aqueous sodium sulfide to remove unreacted sulfur, and was further recrystallized from cyclohexane. The yield was 3.2 g. (52%) of light yellow powder, m.p. 191–194°; the melting point was raised to 199° (dec.) by sublimation at 130° and 2 mm. The compound gives a blood-red color with conc'd nitric acid.

Anal. Calc'd for $C_{12}H_8FNS$: C, 66.3; H, 3.71; N, 6.45.
Found: C, 66.0; H, 3.90; N, 6.43.

Method B. The sample of XXXI prepared in the attempted synthesis of 1,4-difluorophenothiazine (XXXII) melted at 194.5–196°; a mixture melting point with a sample prepared by Method *A* (m.p. 199°) was 195–197°. The infrared spectra of the two samples were identical.

Anal. Calc'd for $C_{12}H_8FNS$: N, 6.45. Found: N, 6.46.

Attempted preparation of 1,4-difluorophenothiazine (XXXII). Several attempts were made to prepare this compound from 2,5-difluorodiphenylamine (X) and sulfur, using the conditions described for XXX, methods *A* and *B*. There was rapid evolution of hydrogen sulfide, but the only compound which ever was isolated from this reaction was a 10% yield of 2-fluorophenothiazine, described in Method *B* under XXXI.

Attempted preparation of 1,3-difluorophenothiazine (XXXIII). The ring closure of 2,4-difluorodiphenylamine (XI) was attempted, but the results were essentially the same as those described in the attempted preparation of 1,4-difluorophenothiazine (XXXII).

2,4-Difluorophenothiazine (XXXIV). Several attempts to prepare XXXIV from the slightly yellow 3,5-difluorodiphenylamine (XII) were unsuccessful; however, using a carefully purified product obtained by recrystallization from 30–60° petroleum ether, a 43% yield of XXXIV was obtained, using the conditions described for XXX except with a 35-minute heating period at 175°; m.p. 129–130° (after sublimation at 130° and 2.5 mm.)

Anal. Calc'd. for $C_{12}H_7F_2NS$: C, 61.3; H, 3.00; N, 5.95.
Found: C, 61.3; H, 2.98; N, 6.16.

Attempted preparation of 1,4,7-trifluorophenothiazine (XXXV) and *1,4,8-trifluorophenothiazine* (XXXVI). Attempts at the ring closure of 2,4′,5-trifluorodiphenylamine (XIV), and 2,3′,5-trifluorodiphenylamine (XIII) both in the open tube and the sealed tube, and with carefully purified amine in both cases, was unsuccessful. In both cases hydrogen sulfide was evolved, but no solid product could be obtained from the red tar resulting from this reaction.

2,4,7-Trifluorophenothiazine (XXXVII). Ring closure of 3,4′,5-trifluorodiphenylamine (XVI) (which was carefully purified, or else no product was obtained) with sulfur and iodine at 190° for one hour gave a 20% yield of XXXVII, m.p. 147–148° (dec.) (after sublimation at 140° and 2.5 mm. followed by recrystallization from cyclohexane).

Anal. Calc'd. for $C_{12}H_6F_3NS$: C, 56.9; H, 2.39; N, 5.53.
Found: C, 57.1; H, 2.40; N, 5.57.

XXXVII gives a blood-red color with conc'd nitric acid.

2,4,8-Trifluorophenothiazine (XXXVIII). A 44% yield of XXXVIII was obtained from 6.1 g. of 3,3′,5-trifluorodiphenylamine (XV), 1.75 g. of sulfur, and a crystal of iodine heated at 170° for 2.5 hours. The material was worked up as described for XXX, and the material was purified by sublimation (at 140° and 2 mm.) and then was recrystallized from cyclohexane; m.p. 142–143°.

Anal. Calc'd for $C_{12}H_6F_3NS$: C, 56.9; H, 2.39; N, 5.53.
Found: C, 56.9; H, 2.42; N, 5.45.

XXXVIII gave a blood-red color with conc'd nitric acid.

2,4,6,8-Tetrafluorophenothiazine (XXXIX). A 13% yield was obtained by heating 1.2 g. of 3,3′,5,5′-tetrafluorodiphenylamine (XVII), 0.31 g. of sulfur, and a crystal of iodine at 230° for a minute or so, then heating at 210° for 20 minutes. The mixture was worked up as described for XXX, the product was recrystallized from carbon tetrachloride, and was sublimed at 135° and 2 mm.; white needles, m.p. 193–193.5°.

The experiment was repeated in a sealed tube heated at 210–240° for 1.5 hours; a 20% yield of XXXIX was obtained in this experiment.

Anal. Calc'd for $C_{12}H_5F_4NS$: C, 53.1; H, 1.86; N, 5.16.
Found: C, 53.3; H, 1.87; N, 5.10, 5.38.

XXXIX reacts slowly with conc'd nitric acid; on standing the crystals turn light red.

3-Trifluoromethylphenothiazine (XL). *Method A.* A solution of 15 g. (0.44 mole) of 2-nitro-2′-formamido-4-trifluoromethyldiphenyl sulfide (XXVI) in 150 ml. of dry acetone was prepared, and to it was added 44 ml. of 1 *N* sodium hydroxide in absolute ethanol; the mixture was refluxed for a half-hour, during which time a precipitate of sodium nitrite was formed.

At the end of the reflux period the solution was filtered, the filtrate was evaporated almost to dryness in a steam-bath, and the residue was taken up in boiling carbon tetrachloride, treated with Norit, filtered, and cooled in an ice-salt bath. A precipitate of 6.0 g. (52%) of XL was formed, m.p. 217–218°. Further recrystallization from carbon tetrachloride did not raise the melting point of the slightly green material.

Anal. Calc'd for $C_{13}H_8F_3NS$: C, 58.4; H, 3.02; N, 5.24.

Found: C, 58.3; H, 3.10; N, 5.36.

Method B. XL was also prepared, in considerably poorer yield, from 2-nitro-2′-benzamido-4-trifluoromethyldiphenyl sulfide (XXIV). The low yield was attributed to difficulties in isolation due to the presence of ethyl benzoate formed as a by-product in the reaction.

XL gives a blood-red color with conc'd nitric acid.

2-Trifluoromethylphenothiazine (XLI). A 59% yield of XLI was obtained from 2-nitro-2′-formamido-5-trifluoromethyldiphenyl sulfide (XXVII) by the method described for XL; m.p. 189–190° in agreement with the literature value (7). The infrared spectrum obtained for this compound was identical with that reported by Smith (7).

3-Fluorophenothiazine (XLII). A 43% yield of XLII was prepared by the method described for XL; m.p. 178–179°, in agreement with that reported by Smith (8). XLII gives a blood-red color with conc'd nitric acid.

Attempted preparation of 4-trifluoromethylphenothiazine (XLIII). A solution of 4.6 g. (0.013 mole) of 2-nitro-2′-formamido-3-trifluoromethyldiphenyl sulfide (XXV) in 46 ml. of acetone was treated as described for XL. Nothing but starting material could be isolated from this experiment. The experiment was repeated, replacing the acetone with carbon tetrachloride; still no product could be obtained. A third experiment was tried in acetone, using a more concentrated solution of sodium hydroxide. This time a slight amount of sodium nitrite precipitated, but only a small amount of syrup was obtained, which gave a blood-red color with nitric acid, indicating that some of the phenothiazine was present. None of it could be obtained from the syrup, however, by treatment with carbon tetrachloride or any other solvent. A fourth attempt using a 1 mole excess of sodium hydroxide gave essentially the same results—an indication that some of the desired product had been formed, but none of it was isolated.

Attempted preparation of 2-fluorophenothiazine (XXXI). A solution of 4.4 g. (0.015 mole) of 2-nitro-2′-formamido-5-fluorodiphenyl sulfide (XXIX) dissolved in 44 ml. of acetone was treated as described for XL. The yellow precipitate (supposedly the eliminated sodium nitrite) was dissolved in water and treated with Norit; this solution gave a faint positive test for nitrite ion, but with calcium chloride it gave a strongly positive test for fluoride ion.

The acetone was evaporated from the filtrate, and an orange precipitate formed. This had a melting point of 160–170°, gave a green color with concentrated nitric acid, and contained nitrogen and sulfur, but no fluorine. A nitrogen analysis showed 7.0% nitrogen. The material resisted all further attempts at purification, and the material was not further characterized. The experiment was repeated, with essentially the same results.

Infrared analysis. The infrared spectra were made with a Baird Double-Beam Recording Infrared Spectrophotometer. Samples were run in the solid state in some cases by dripping solutions of the compounds in benzene on mull plates and allowing the solvent to evaporate; the resulting smear gave curves that were as good as those run in a Nujol mull. Other spectra were obtained by the micro technique using solid KBr pellets; this procedure was found to be far superior to the smear technique, particularly in the region between 2 and 10 microns.

SUMMARY

This paper reports the preparation of a number of fluorophenothiazines; they are 1-fluoro-, 2-fluoro-, 2,4-difluoro-, 2,4,7-trifluoro-, 2,4,8-trifluoro-, 2,4,6,8-tetrafluoro-, and 3-trifluoromethyl-phenothiazine. Most of these were

prepared by thionation of the appropriate diphenylamines; the last one in the list was prepared by a Smiles rearrangement. 3-Fluoro- and 2-trifluoromethylphenothiazine, previously known, were prepared by new methods; in addition, the attempted preparation of several fluorophenothiazines both by thionation of the diphenylamines and by the Smiles rearrangement is reported. In the course of the work a number of new fluorodiphenylamines, fluorodiphenyl sulfides, and other intermediates were prepared. The infrared spectra of these and other fluorophenothiazines were obtained, and an attempt was made to see if a reliable method of structure determination of fluorophenothiazines could be made using infrared spectra; it was decided that the use of the infrared for structure determination should be approached with caution.

An improved procedure for the preparation of *m*-difluorobenzene from *m*-phenylenediamine was developed.

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