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Synthesis of Phenothiazines. V.[1] Some Halogen-Containing Phenothiazines[2]

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Six new halogen-containing disubstituted phenothiazines have been prepared. The tendency of some of these compounds to form addition compounds with sulfur is described. Infrared data are presented and discussed. An improved synthesis of 1-chlorophenothiazine is given.

Various halogen-containing phenothiazines were prepared as part of a continuing investigation of new psychopharmacological agents. The new phenothiazines are: 2-fluoro-8-trifluoromethylphenothiazine, 3-methyl-8-trifluoromethylphenothiazine, 3-methoxy-6-trifluoromethylphenothiazine, and 2-chloro-7-fluorophenothiazine. Two additional methoxytrifluoromethyl-phenothiazines have been isolated whose structures are still unknown. An attempt to prepare 2-chloro-3,7-difluorophenothiazine was unsuccessful.

The phenothiazines were synthesized by iodine-catalyzed thionation of appropriate diphenylamines.[6,7] The diphenylamines were prepared by means of the Weston and Adkins[8] modification of the Goldberg[9] reaction. This modification, which eliminates the use of a solvent, led to considerably higher yields of 3,3'-bis(trifluoromethyl)diphenylamine[10] and 3-methyl-3'-trifluoromethyldiphenylamine than those previously reported.[11] The new diphenylamines are listed in Table I.

The course of the thionations was quite dependent on time, temperature, iodine concentration, and reaction scale. During the investigation of these variables several unusual compounds were isolated which seemed to be the desired phenothiazines in combination with even numbers of sulfur atoms. These crystalline compounds could be sublimed *in vacuo* or recrystallized without change. Thus, thionation of 3-fluoro-3'-trifluoromethyldiphenylamine (I) with sulfur and 3% iodine (based on I) produced a 12% yield of white 2-fluoro-8-trifluoromethylphenothiazine (II), m.p. 159.5–160°. Thionation of I could not be initiated using 1% iodine. When the amount of iodine was increased to 5%, product II was not obtained. Instead a small amount of yellow crystals (III), melting at 149–151° after sublimation *in vacuo*, was the only product isolated. Elemental analysis indicated that III was an addition compound of II with two atoms of sulfur.

Iodine catalyzed (1%) thionation of 4-methyl-3'-trifluoromethyldiphenyl-amine (IV) yielded a very pale yellow solid (V) which melted at 202–203° after vacuum sublimation. Recrystallization of V from carbon tetrachloride did not change its melting point. Elemental analysis indicated a methyltrifluoromethylphenothiazine in combination with six atoms of sulfur. Changing the recrystallizing solvent from carbon tetrachloride to benzene produced pale yellow crystals of pure 3-methyl-8-trifluoromethylphenothiazine (VI), m.p. 216–217°.

Efforts to effect thionation of 0.03 mole of 3-methoxy-3'-trifluoromethyl-diphenylamine (VII) in the presence of 2 and 5% iodine gave only traces of a phenothiazine. When 3% iodine was used with 0.03 mole of VII, a 7% yield of pale yellow glistening platelets (VIII) was obtained, melting at 173.2–173.5°. Repeated crystallization from benzene did not change the melting point. Elemental analysis indicated a methoxytrifluoromethylphenothiazine in combination with four atoms of sulfur. Changing the recrystallizing solvent from benzene to carbon tetrachloride provided a pure methoxytrifluoromethylphenothiazine (IX), m.p. 179–180°. The infrared spectra of VIII and IX were identical.

On a 0.3-mole scale (instead of 0.03 mole) it was possible to initiate thionation of VII with as little as 1.5% iodine. The major product was an 18% yield of very pale yellow glistening plates of a pure methoxytrifluoromethylphenothiazine (X), m.p. 137.5–139.0°. The infrared spectra of IX and X were almost identical. In addition, a trace of a phenothiazine was isolated which melted above 170°.

Although many investigators have attempted to correlate the infrared spectrum and the structure of monosubstituted phenothiazines[1,11–17] relatively

(1) Paper III, Edward A. Nodiff, Sidney Lipschutz, Paul N. Craig, and Maxwell Gordon, *J. Org. Chem.*, 25, 60 (1960). Paper IV, Paul N. Craig, Maxwell Gordon, John J. Lafferty, B. M. Lester, Alex Pavloff, and Charles L. Zirkle, *J. Org. Chem.*, 25, 944 (1960).

(2) These compounds were prepared at the Research Institute of Temple University under a contract with Smith Kline and French Laboratories.

(3) Research Institute of Temple University.

(4) To whom inquiries may be addressed.

(5) Smith Kline and French Laboratories.

(6) A. Bernthsen, *Ber.*, 16, 2896 (1883); *Ann.*, 230, 73 (1885).

(7) E. Knoevenagel, *J. Prakt. Chem.*, (2), 89, 11 (1914).

(8) P. E. Weston and H. Adkins, *J. Am. Chem. Soc.*, 50, 859 (1928).

(9) I. Goldberg, *Ber.*, 40, 4541 (1907).

(10) N. L. Smith, *J. Org. Chem.*, 16, 415 (1951).

(11) N. L. Smith, *J. Org. Chem.*, 15, 1125 (1950).

(12) P. Charpentier, P. Gailliot, and J. Gaudechon, *Compt. rend.*, 232, 2232 (1951).

TABLE I

PREPARATION AND PROPERTIES OF THE DIPHENYLAMINES

Diphenylamine	Acetanilide Used	Bromobenzene Used	M.P.	B.P.	Mm.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-Cl-4,4'-di-F	3-Cl-4-F[a]	4-F[b]	56.5–57[f]	145–150	1	30	60.14	3.46		59.85	3.58	
4-CH_3-3'-CF_3	3-CF_3[c]	4-CH_3	66–67[f]			54	66.92	4.81	5.58	67.13	5.10	5.62
3-CH_3O-3'-CF_3	3-CH_3O	3-CF_3[d]		148–148.5[g]	0.5	72	62.92	4.53		62.73	4.61	
3-F-3'-CF_3	3-F[e]	3-CF_3[d]		135–135.5[h]	2	62	61.18	3.55	5.49	61.36	3.76	5.53

[a] I. J. Rinkes, *Chem. Weekblad*, 11, 360 (1914). [b] A. Roe, *Org. Reactions*, 5, 212 (1949). [c] F. Swarts, *Bull. Acad. roy. Belg.* (3) 35, 375 (1898). [d] J. Simons and E. Ramler, *J. Am. Chem. Soc.*, 65, 389 (1943). [e] T. de Crauw, *Rec. trav. chim.*, 48, 1061 (1929). [f] From petroleum ether (b.p. 30–60°). [g] n_D^{30} 1.5630. [h] n_D^{21} 1.5521.

TABLE II

INFRARED SPECTRA OF SOME DISUBSTITUTED PHENOTHIAZINES BETWEEN 11.0 AND 13.5 μ

Phenothiazine	M.P.	Peaks between 12.0 and 12.5 μ	Peaks between 12.5 and 13.1 μ	Other Peaks between 11.0 and 13.5 μ
8-F-2-CF_3	159.5–160	12.15, 12.45		11.50, 11.85, 13.20(w)
8-CH_3-3-CF_3	216–217	12.15, 12.30		11.50, 13.10(w)
8-CH_3-2-CF_3[a]	227–228	12.20, 12.40		11.20(w), 11.55, 12.70(w), 13.30
?-CH_3O-?-CF_3	179–180	12.30	12.70	11.20(w), 11.55, 11.80, 13.30(w)
?-CH_3O-?-CF_3	137.5–139	12.25	12.65	11.20(w), 11.55, 11.80, 13.30(w)
3-CH_3O-8-CF_3[b]	169–170	12.10, 12.30		11.20(w), 11.60, 11.75, 13.10
3-CH_3O-6-CF_3[c]	95–96	12.45	12.80	11.25(w), 11.50, 11.80(w), 12.10(w), 13.00(w)
2-Cl-8-CF_3[b]	188–189	12.15, 12.35		11.55, 11.80, 12.95(w)
2-Cl-7-F	179–180	12.40, 12.50		11.05, 11.55, 11.75, 13.40

[a] N. L. Smith, *J. Org. Chem.*, 15, 1125 (1950). [b] P. N. Craig, *et al.*, *J. Org. Chem.*, 22, 709 (1957). [c] The residues from the synthesis of 3-methoxy-8-trifluoromethylphenothiazine, were distilled to give a 2% yield of the isomeric, 3-methoxy-6-trifluoromethylphenothiazine, b.p. 175–180°/0.1 mm. The analytical sample, m.p. 95–96°, was obtained by crystallization from petroleum ether (b.p. 30–75°).

Anal. Calcd. for $C_{14}H_{10}F_3NOS$: C, 56.56; H, 3.39; N, 4.71. Found: C, 56.45; H, 3.92; N, 5.00.

little has been published, in this vein, regarding the phenothiazines with a substituent in each benzene ring.[16,17] The 2- or 3-substituted phenothiazines usually have a peak between 12.0 and 12.5 μ, and the 1- or 4-substituted phenothiazines usually have a peak between 12.5 and 13.1 μ.

The compounds II and VI have two strong bands in the region 12.0–12.5 μ and have either no bands or weak bands in the 12.5–13.1 μ region. These compounds have therefore been tentatively assigned the structures of 2-fluoro-8-trifluoromethylphenothiazine and 3-methyl-8-trifluoromethylphenothiazine (Table II). Table II also includes maxima for some disubstituted phenothiazines which have been described in the literature, but for which no infrared data were given. As anticipated, those phenothiazines containing two asymmetrically trisubstituted benzene rings (2-methyl-8-trifluoromethylphenothiazine, 3-methoxy-8-trifluoromethylphenothiazine, and 2-chloro-8-trifluoromethylphenothiazine) exhibit two strong peaks in the region 12.0–12.5 μ and none in the 12.5–13.1 μ region. 3-Methoxy-6-trifluoromethylphenothiazine, with one asymmetric and one vicinal trisubstituted ring has one strong peak at 12.45 μ and another at 12.8 μ.

The two isomeric phenothiazines (IX and X) which were isolated from the thionation of 3-methoxy-3'-trifluoromethyldiphenylamine (VII) have almost identical spectra which include strong peaks at 12.3 and 12.7 μ. Infrared data would therefore seem to indicate that both IX and X have a combination of vicinal and asymmetric trisubstitution in the same molecule and represent the structures 4-methoxy-8-trifluoromethylphenothiazine and 2-methoxy-6-trifluoromethylphenothiazine. It is not possible at present to assign definite structures to IX and X.

An attempt to synthesize the desired 2-methoxy-8-trifluoromethylphenothiazine *via* an unambiguous Smiles synthesis, as shown below, was unsuccessful.

Rearrangement of XII occurred, but the resulting thiol (XIII) could not be cyclized. On standing overnight exposed to air at room temperature XIII was oxidized to the disulfide (XIV).

It was not possible to prepare 2-chloro-3,7-difluorophenothiazine by treating 3-chloro-4,4'-difluorodiphenylamine with sulfur and iodine. Thionation was invariably accompanied by loss of a fluorine atom[18] and by the formation, in yields of 10% or less, of a phenothiazine containing one chlorine atom and one fluorine atom. The elimina-

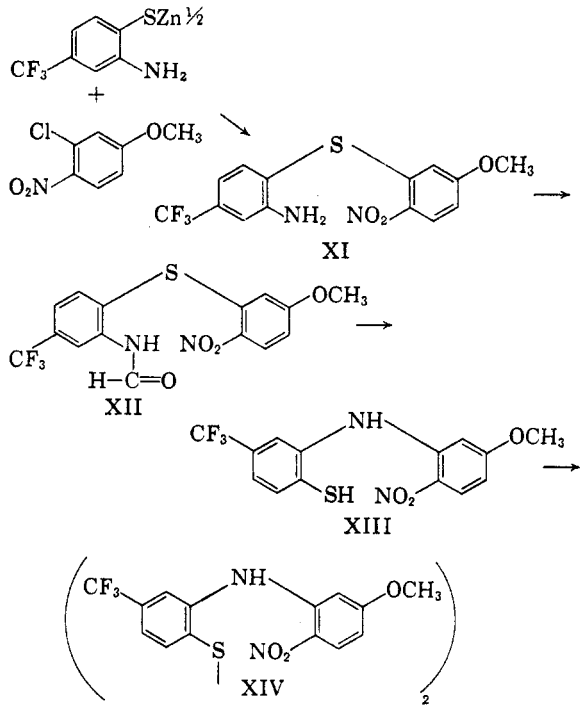
(13) J.-P. Bourquin, G. Schwarb, G. Bamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Reiz, *Helv. Chim. Acta*, 41, 1061 (1958).

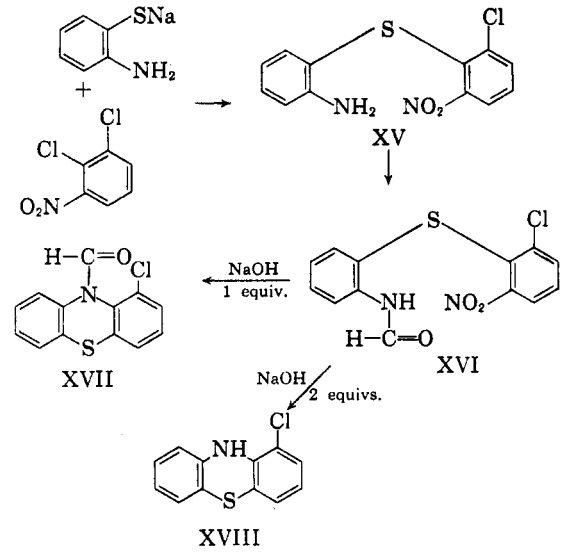
(14) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, 79, 4375 (1957).

(15) S. P. Massie, *Chem. Revs.*, 54, 797 (1954).

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

(17) J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, 9, 397 (1956).





tion of catalyst or the substitution of aluminum chloride[19] for iodine were of no help. Variation of time, temperature, and catalyst concentration and the use of sulfur dichloride as thionating agent[20] were likewise unsuccessful. Since the fluorine atom *ortho* to the chlorine atom is relatively labile, the isolated phenothiazine was therefore most probably 2-chloro-7-fluorophenothiazine. In favor of this structure is the presence, in the infrared spectrum, of two strong peaks at 12.40 and 12.50 μ (Table II).

During the present investigation it was necessary to prepare 1-chlorophenothiazine (XVIII). Two syntheses of XVIII had been previously reported; by dehydrohalogenation of 2-amino-2′-bromo-3-chlorodiphenylsulfide[21] and by the thionation of 2-chlorodiphenylamine.[22] In this laboratory an improved method was used which involved Smiles rearrangement[23,24] of 6-chloro-2′-formamido-2-nitrodiphenylsulfide (XVI). This method used inexpensive commercial starting materials and required only three simple steps as follows:

The infrared spectrum of XVIII showed a weak peak at 12.8 μ and strong peaks at 13.1 μ and 13.4 μ. The latter peaks are characteristic of the combination of vicinal trisubstituted and *o*-disubstituted benzene rings which is found in 1- or 4-substituted phenothiazines. There were no peaks in the region 12.0–12.5 μ.

EXPERIMENTAL[25]

Preparation of the diphenylamines. All the diphenylamines listed in Table I were prepared as shown below for 3-methoxy-3-trifluoromethyldiphenylamine.

A mixture of 16.5 g. (0.1 mole) of 3-methoxyacetanilide, 33 g. (0.15 mole) of 3-bromobenzotrifluoride, 8.4 g. (0.06 mole) of anhydrous potassium carbonate, and 0.34 g. of copper-bronze powder was stirred for 24 hr. under reflux, in a bath maintained at 240° (internal temp. 215°). The mixture was allowed to cool to room temperature and extracted with acetone. The acetone was removed under reduced pressure and the dark brown slightly viscous residue was refluxed for 4 hr. with 100 ml. of 20% ethanolic potassium hydroxide. The mixture was poured into 200 ml. of saturated salt solution and extracted with ether. The ether was removed under reduced pressure and the residue was distilled to give 19.1 g. (72%) of yellow oil; b.p. 148–148.5° (0.5 mm.); n_D^{30} 1.5630.

2-Fluoro-8-trifluoromethylphenothiazine (II). A mixture of 7.65 g. (0.03 mole) of 3-fluoro-3′-trifluoromethyldiphenylamine (I), 1.73 g. (0.054 mole) of sulfur, and 0.23 g. of iodine was maintained at 150° for 2.5 hr. The dark brown semisolid reaction mass was dissolved in 100 ml. of boiling benzene and the solution was concentrated under reduced pressure, after treatment with decolorizing carbon. Pale yellow crystals separated which, after two recrystallizations from benzene, gave 0.96 g. (12%) of pure white crystals; m.p. 159.5–160°. Compound II produced a deep red color with concentrated nitric acid.[26]

Anal. Calcd. for $C_{13}H_7F_4NS$: C, 54.73; H, 2.47; N, 4.91. Found: C, 54.94; H, 2.66; N, 5.04.

(18) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick (*Australian J. Chem.*, 8 (2), 252 (1955)) have observed similar removal of halogen during the thionation of 4-chloro- and 4-fluorodiphenylamine.

(19) F. Ackermann, *Fortschr. Teerfarbenfabrikation*, 10, 144 (1910).

(20) E. Holzmann, *Ber.*, 21, 2056 (1888).

(21) P. J. C. Buisson, P. Gaillot, and J. Gaudechon, U. S. Patent 2,769,002 (1956).

(22) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, 21, 347 (1956).

(23) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).

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

(25) All melting and boiling points are uncorrected. Analyses are by the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories.

(26) This color reaction was characteristic of all of the phenothiazines and phenothiazine addition compounds prepared during these investigations.

Using 1% of iodine as catalyst, thionation of I could not be initiated even though the temperature was raised as high as 250°. With 5% of iodine, thionation of I was carried out as follows:

A mixture of 2.55 g. (0.01 mole) of I, 0.58 g. (0.018 mole) of sulfur, and 0.13 g. of iodine was maintained at 135–140° for 1.5 hr. The reaction mass was dissolved in boiling benzene; the solution was treated with Norit and concentrated under reduced pressure to give 0.6 g. of tan solid. Vacuum sublimation at 0.05 mm. and 120° followed by recrystallization from petroleum ether yielded 0.1 g. of yellow crystals (III); m.p. 149–151°.

Anal. Calcd. for $C_{13}H_7F_4NS_2$ (II + 2 sulfur atoms): C, 44.65; H, 2.01; S, 27.5. Found:[27] C, 44.12; H, 2.19; S, 34.62, 33.70, 35.23.

3-Methyl-8-trifluoromethylphenothiazine (VI). A mixture of 75 g. (0.3 mole) of 4-methyl-3′-trifluoromethyldiphenylamine (IV), 17.3 g. (0.54 mole) of sulfur, and 0.75 g. of iodine was maintained for 1.5 hr. at 150–160° and for 0.5 hr. at 170°. After cooling to room temperature, the reaction mixture was extracted with benzene, the extracts were concentrated, and the resulting yellow solid, m.p. 215–217°, was recrystallized from benzene; m.p. 216–217°; yield 15.2 g. (18%).

Anal. Calcd. for $C_{14}H_{10}F_3NS$: C, 59.77; H, 3.58; N, 4.98. Found: C, 59.83; H, 3.88; N, 4.96.

In a similar thionation, a mixture of 2.51 g. (0.01 mole) of IV, 0.58 g. (0.018 mole) of sulfur, and 25 mg. of iodine was raised from 150° to 230° during 3 hr. and maintained at 230° for 15 min. No etching was visible on the reaction vessel. The reaction mixture was recrystallized from carbon tetrachloride (Norit) and sublimed *in vacuo* to give a yellow solid; m.p. 202–203°. Subsequently, another recrystallization from carbon tetrachloride gave pale yellow crystals with unchanged melting point.

Anal. Calcd. for $C_{14}H_{10}F_3NS_7$ (VI + 6 sulfur atoms): C, 35.50; H, 2.11; N, 2.96; S, 47.5: Found:[27] C, 34.65; H, 2.42; N, 2.87; S, 51.22, 50.78, 52.55.

Thionations of 3-methoxy-3′-trifluoromethyldiphenylamine (VII). A mixture of 8.0 g. (0.03 mole) of VII, 1.73 g. (0.054 mole) of sulfur, and 0.24 g. of iodine (3% of VII) was maintained at 130–140° for 1 hr. and 140–155° for another hour. The reaction mixture, a dark brown viscous liquid at room temperature, was dissolved in 100 ml. of boiling benzene and decolorized by stirring with activated alumina. Concentration under reduced pressure gave pale yellow platelets; m.p. 168.0–168.5°. Recrystallization from benzene–petroleum ether (b.p. 30–65°) gave pale yellow glistening platelets; m.p. 173–173.5°. Another recrystallization from pure benzene did not change the melting point. Analysis indicates a methoxytrifluoromethylphenothiazine in combination with four sulfur atoms; yield 0.6 g. (7%).

Anal. Calcd. for $C_{14}H_{10}F_3NOS_5$: C, 39.60; H, 2.36; N, 3.30; S, 37.8. Found:[27] C, 38.95; H, 2.31; N, 3.38; S, 39.19, 35.38, 38.60.

Changing the crystallizing solvent from benzene to carbon tetrachloride gave glistening pale yellow platelets of a methoxytrifluoromethylphenothiazine; m.p. 179–180°.

Anal. Calcd. for $C_{14}H_{10}F_3NOS$: C, 56.56; H, 3.39. Found: C, 56.56; H, 3.47.

In another thionation, a mixture of 93.5 g. (0.35 mole) of VII, 22.4 g. (0.70 mole) of sulfur and 1.4 g. (1.5% of VII) of iodine was maintained at 175–180° for 2 hr. The reaction mixture was dissolved in carbon tetrachloride and decolorized by stirring with activated alumina. Concentration under reduced pressure gave glistening pale yellow plates; m.p. 136–138°. Vacuum sublimation followed by recrystallization from benzene gave light yellow glistening platelets; m.p. 137.5–139°; yield 19 g. (18%). Analysis indicates a pure methoxytrifluoromethylphenothiazine.

Anal. Calcd. for $C_{14}H_{10}F_3NOS$: C, 56.56; H, 3.39. Found: C, 56.71; H, 3.56.

A small quantity of material giving a positive phenothiazine color test and melting above 170° was also isolated during the latter thionation, but the small quantity precluded further characterization.

2-Amino-5′-methoxy-2′-nitro-4-trifluoromethyldiphenylsulfide (XI). A slurry of the zinc salt of 2-amino-4-trifluoromethylbenzenethiol[28] (5.2 g., 0.0113 mole) in 55 ml. of ethanol was mixed at room temperature, under nitrogen, with 0.023 mole of sodium ethoxide in 25 ml. of ethanol. To the resulting suspension was added 4.29 g. (0.023 mole) of 3-chloro-4-nitroanisole[29] in 55 ml. of ethanol and the mixture was refluxed overnight. The mixture was filtered and the filtrate concentrated under reduced pressure. The brown solid residue was recrystallized from ethanol-water to give yellow crystals of XI; m.p. 138–140.5°; yield 3.0 g. (38%). An analytical sample was obtained by vacuum sublimation followed by recrystallization from ether–petroleum ether (b.p. 20–40°); m.p. 139.5–141°.

Anal. Calcd. for $C_{14}H_{11}N_2O_3SF_3$: C, 48.83; H, 3.22. Found: C, 48.80; H, 3.55.

2-Formamido-5′-methoxy-2′-nitro-4-trifluoromethyldiphenylsulfide (XII). A mixture of 3 g. of XI and 30 g. of 90% formic acid was refluxed overnight. The dark brown suspension was poured over ice. The resulting brown solid was recrystallized from methanol to give 1.5 g. (47%) of ivory needles; m.p. 188.5–190°.

Anal. Calcd. for $C_{15}H_{11}N_2O_4SF_3$: C, 48.39; H, 2.98. Found: C, 48.13; H, 3.35.

Smiles rearrangement of XII. To a clear, pale yellow solution of 0.9 g. (0.0026 mole) of XII in 10 ml. of acetone were added 5.2 ml. of 1*N* ethanolic sodium hydroxide. The solution turned orange immediately and then became very deep red during 15 min. refluxing. Refluxing was continued for 75 min., a white, water-soluble solid was removed, and the filtrate was concentrated under reduced pressure. The resulting dark red solid was dissolved in ethanol and the red solution was acidified with dilute hydrochloric acid. The red color was immediately replaced by yellow, and on scratching, there separated yellow crystals of 2-mercapto-5′-methoxy-2′-nitro-5-trifluoromethyldiphenylamine (XIII); m.p. 114–115°. Recrystallization from ethanol did not change this melting point.

Anal. Calcd. for $C_{14}H_{11}N_2O_3SF_3$: C, 48.83; H, 3.22; N, 8.14. Found: C, 48.77; H, 3.69; N, 8.21.

On standing overnight, exposed to air at room temperature, the filtrate from the recrystallization of XIII turned green and deposited orange crystals of the disulfide XIV. After boiling the crystals with ethanol to remove traces of XIII, the melting point was 163–164°.

Anal. Calcd. for $C_{28}H_{20}N_4O_6S_2F_6$: C, 48.98; H, 2.94. Found: C, 49.06; H, 3.28.

Thionation of 3-chloro-4,4′-difluorodiphenylamine. A mixture of 7.19 g. (0.03 mole) of 3-chloro-4,4′-difluorodiphenylamine, 1.73 g. (0.054 mole) of sulfur and 0.20 g. of iodine was maintained at 155° for 6 hr. Etching of the glass reaction vessel indicated the loss of fluorine. Benzene extraction of the reaction mixture provided 2.8 g. of yellow-brown solid which did not crystallize well from the usual solvents and solvent combinations. Vacuum sublimation at 0.05 mm. and 150–160° gave 0.7 g. of white solid, m.p. 179–180°.

Anal. Calcd. for $C_{12}H_7ClFNS$: C, 57.23; H, 2.78. Found: C, 57.51; H, 3.16.

2′-Amino-6-chloro-2-nitrodiphenylsulfide (XV). A solution of 153.6 g. (0.80 mole) of 2,3-dichloronitrobenzene in 1 l. of absolute ethanol was added to a solution of 32 g. (0.80

(27) Duplicate determinations of carbon, hydrogen, and nitrogen provided excellent checks. Although the sulfur analyses (Carius) showed considerable variation, they indicate that the sulfur content is of the right order of magnitude.

(28) A. I. Kiprianov and L. M. Yagupolsky, *Zhur. obschchei Khim.*, 22, 2209 (1952).

(29) H. E. Ungnade and I. Ortega, *J. Org. Chem.*, 17, 1475 (1952).

mole) of sodium hydroxide, 240 ml. of water, 100 g. (0.80 mole) of *o*-aminothiophenol and 1.8 l. of absolute ethanol. The mixture was stirred at room temperature for 5 min. when sodium chloride suddenly precipitated. The reaction mixture was then stirred and refluxed for 2 hr. and filtered while hot. The filtrate was heated to boiling and 800 ml. of water were added with vigorous stirring. Almost immediately orange needles formed; m.p. 126–127°; 197 g.; (88%). Two recrystallizations from ethanol did not change the melting point.

Anal. Calcd. for $C_{13}H_9ClN_2O_2S$: C, 51.34; H, 3.23. Found: C, 51.46; H, 3.38.

6-Chloro-2'-formamido-2-nitrodiphenylsulfide (XVI). A mixture of 197 g. (0.7 mole) XV and 2 kg. of 90% formic acid was refluxed for 10 hr., cooled to room temperature, and poured over 2 l. crushed ice. The green gum soon solidified to a yellow-green solid. Recrystallization from aqueous ethanol (Norit) gave an orange-yellow solid, which after three recrystallizations from absolute ethanol, gave 142 g. (66%) of yellow crystals; m.p. 124–125°.

Anal. Calcd. for $C_{13}H_9ClN_2O_3S$: C, 50.57; H, 2.94. Found: C, 50.50; H, 3.02.

1-Chloro-10-formylphenothiazine (XVII). To the yellow solution of 6.2 g. (0.02 mole) XVI in 75 ml. of acetone were added 20 ml. of 1*N* ethanolic sodium hydroxide. The color changed immediately from yellow to orange and sodium nitrite precipitated. The mixture was refluxed for 2 hr. and the solid was removed. Concentration of the filtrate gave a maroon oil which solidified on standing overnight. Recrystallization from ethanol yielded 2.4 g. (52%) of XVII as a white solid; m.p. 112–113°; which gave a green color with concentrated nitric acid.

Anal. Calcd. for $C_{13}H_8ClNOS$: C, 59.70; H, 3.08; N, 5.36; Cl, 13.60. Found: C, 59.82; H, 3.24; N, 5.45; Cl, 13.60.

1-Chlorophenothiazine (XVIII). To a solution of 62 g. (0.2 mole) XVI in 750 ml. of acetone was added 400 ml. of 1*N* ethanolic sodium hydroxide. Immediately precipitation of sodium nitrite occurred. The reaction mixture was refluxed for 2.5 hr. and the solid was filtered. Concentration under reduced pressure gave a pale-brown solid. Crystallization from carbon tetrachloride followed by recrystallization from ethanol gave 20 g. (43%) of white crystals of XVIII; m.p. 92–93° (lit.[21,22] m.p. 92–93°).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Reaction of Ethylenethiourea with Phenacyl and *para*-Substituted Phenacyl Halides

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Phenacyl and *para*-substituted phenacyl halides react with ethylenethiourea in acetone at room temperature to yield 2-phenacylmercapto-2-imidazolinium halides (I). Treatment of an aqueous solution of this salt with ammonium hydroxide yields the corresponding free base, 2-phenacylmercapto-2-imidazoline (II). When the *para* group is hydrogen, bromine, methyl mercapto or phenyl, the infrared spectra of these salts show a carbonyl absorption in the 5.9 to 6.0 μ region, the accepted position for an aryl carbonyl; however, when the *para* group is chlorine or nitro the spectra show a complete absence of a carbonyl absorption. In the case of *p*-chloro and *p*-nitro this, along with other evidence, indicates that these salts exist in the enol form in the crystalline state. In general the electronic nature of the *para* group is the determining factor as to whether the salt exists in the keto or enol form. The free bases (II) exist entirely in the enol form regardless of the *para* substituent. In this case the enol derives stability through resonance with the imidazoline portion of the molecule. The original salt in each case can be regenerated from the free base by dissolving a small amount of the base in sufficient acetone and adding 47% hydrobromic acid to yield the bromide or concentrated hydrochloric acid for the chloride. The infrared spectra of salts prepared in this manner from the free bases, are identical with the spectra of the original salts formed. In refluxing ethanol phenacyl halides and ethylenethiourea react to form the bicyclic 3-phenyl-5,6-dihydroimidazo[2,1-*b*]-thiazolium halide (III). Treatment of an aqueous solution of this salt with ammonium hydroxide yields the free base 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (IV). 2-Phenacylmercapto-2-imidazolinium halide (I) (formed in acetone at room temperature) can be converted to the thiazolium type halide (III) by refluxing in ethanol, showing therefore that the salt type I is an intermediate in the formation of III in this reaction.[2]

A number of alkyl isothioureas have been reported[3]; however, relatively few *S*-alkyl derivatives of ethylenethiourea are known (2-alkylmercapto-2-imidazolines). Schacht[4] prepared the methyl and ethyl derivatives by treating ethylenethiourea with the corresponding alkyl halide. Easton and

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(2) Four basic structures will be described throughout the text (I–IV). I and III are salts, the former *via* acetone as solvent and the latter in ethanol. II and IV are the neutral or free bases of I and III respectively. Salts of type I are the open form while III is closed (bicyclic). Subscripts denote the *para* substituent of the benzene ring—this substituent being determined by the *para*-substituted phenacyl halide used in the particular reaction, *e.g.* I_H or II_{NO_2}. At times the anion of the salts of I and III will be shown, *e.g.* I_HCl or $I_{NO_2}Br$. If no anion is designated Br is understood; this will also apply to the subscript for hydrogen.

(3) T. B. Johnson and J. M. Sprauge, *J. Am. Chem. Soc.*, 58, 1348 (1939).

(4) W. Schacht, *Arch. Phar.*, 235, 445 (1897).