Alcoholation of the Trifluoromethyl Group. I. Ortho Esters Derived from 1- and 3-Trifluoromethylphenothiazines (1).

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The preparation of 1-trifluoromethylphenothiazine is reported. Methanolic basic hydrolysis of 1- and 3-trifluoromethylphenothiazines to the corresponding ortho esters of phenothiazinecarboxylic acids is described.

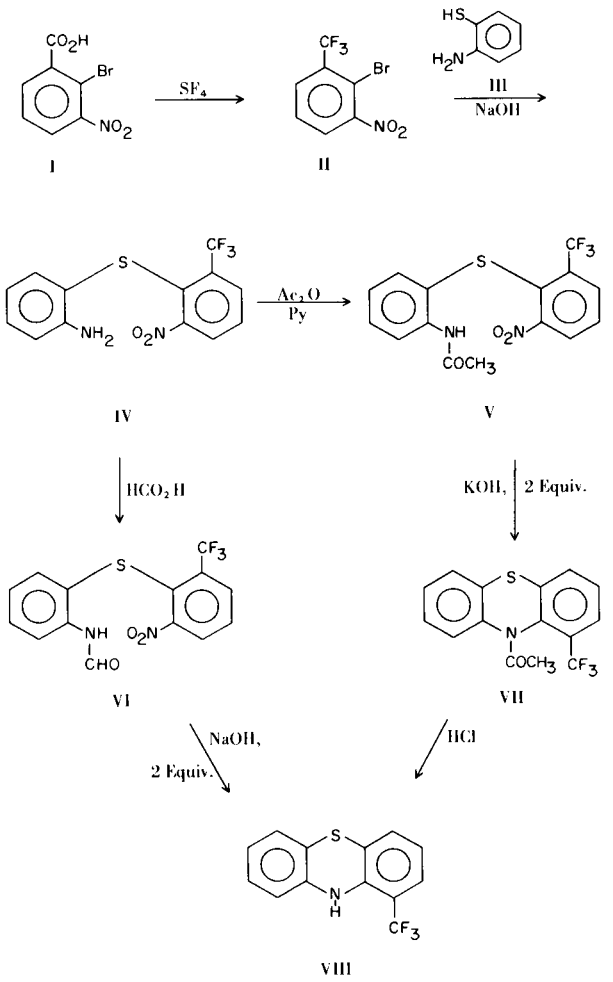
2-, 3- and 4-Trifluoromethylphenothiazines have received considerable attention in past years due mainly to the interest in their antioxidant properties and to the psychotropic action of their derivatives (2-9). As part of a continuing program to develop new pharmacological agents, we required the hitherto unreported 1-trifluoromethyl isomer. We now wish to report the synthesis of 1-trifluoromethylphenothiazine by the Smiles rearrangement (10) and the preparation of a new class of compounds, ortho esters of phenothiazinecarboxylic acids, by the basic hydrolysis [$CF_3 \rightarrow C(OCH_3)_3$] of 1- and 3-trifluoromethylphenothiazines in methanol.

Our approach to 1-trifluoromethylphenothiazine (VIII, Scheme 1) commenced with the preparation of 2-bromo-3-nitrobenzotrifluoride (II). The latter was obtained in good yield from 2-bromo-3-nitrobenzoic acid (I) and sulfur tetrafluoride afforded the appropriate diphenylsulfide (IV) for the Smiles synthesis of VIII.

Although 1- and 4-substituted derivatives of phenothiazine are low melting solids in relation to the 2- and 3-isomers (11), 1-trifluoromethylphenothiazine (VIII) was obtained as an oil which was induced to crystallize (m.p. 28.5-30°) after two months at room temperature. To the best of our knowledge, VIII is the lowest melting phenothiazine without a 10-substituent that has been reported to date. The unusually low melting points of compounds containing a CF_3 group *ortho* to the NH function have been observed previously and have been rationalized in terms of intramolecular hydrogen bonding (12-15).

Interest in the reactivity of fluorine compounds prompted us to investigate the hydrolytic stability of 1-trifluoromethylphenothiazine (VIII). It is a well known fact that the normally refractory CF_3 group can be hydrolyzed to the corresponding carboxylic acid by strong acids at elevated temperatures (16). Furthermore, in the presence of activating groups, alkaline hydrolysis occurs with loss of fluoride ion to yield a carboxylic acid, polymeric material or, with alkaline Raney nickel (17), the corresponding methyl derivative.

SCHEME 1

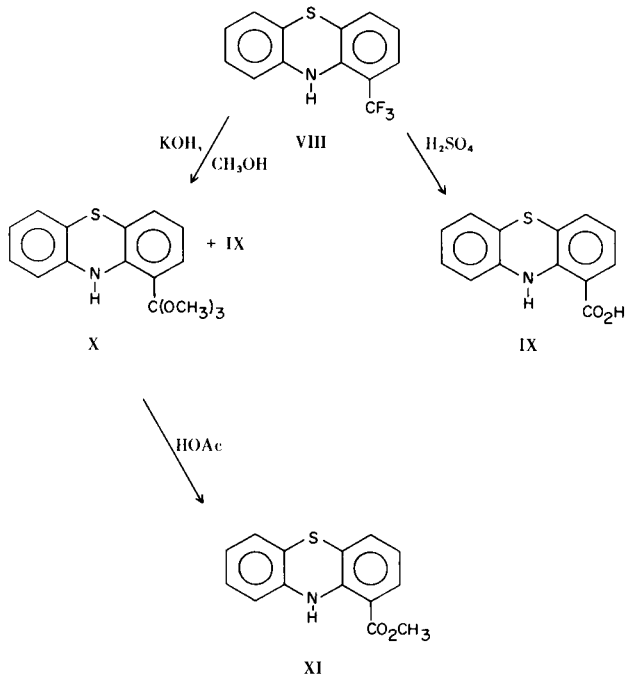


As expected, acid hydrolysis of 1-trifluoromethylphenothiazine (VIII) provided the known carboxylic acid (IX, Scheme 2). Unexpectedly, however, the reaction of VIII and methanolic potassium hydroxide produced an additional product, trimethyl orthophenothiazine-1-carboxylate (X), in 47% yield. There appears to be no previous

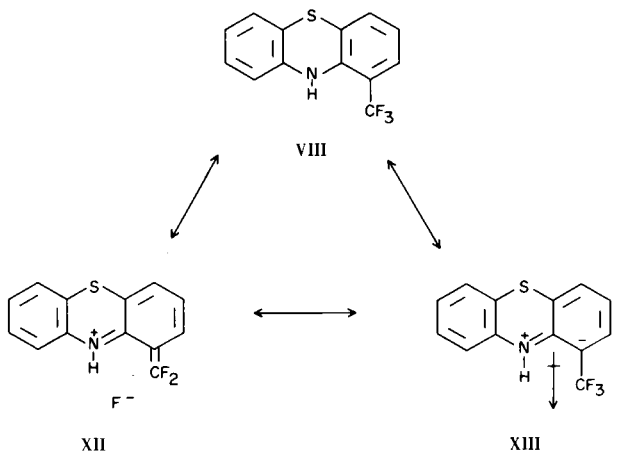
report of such ortho ester formation in reactions of aromatic trifluoromethyl derivatives, although an ortho ester type compound [$Ar_2CHC(OR)_3$ or $AR_2CHCF(OR)_2$] was postulated in the basic hydrolysis of 1,1,1-trifluoro-2,2-diarylethanes (18). The formation of ortho esters from trihalomethyl compounds was reviewed earlier in the aliphatic series (19), but has been observed only recently in aromatic compounds in the basic alcoholysis of benzotrichloride and its *p*-chloro derivative (20).

Confirmation of X was obtained through ir, nmr and elemental analyses. The ortho ester (X) readily underwent acid hydrolysis to methyl phenothiazine-1-carboxylate (XI).

SCHEME 2



The novel conversion of 1-trifluoromethylphenothiazine (VIII) to the ortho ester (X) is in accord with earlier observations (16) concerning the activating influence of amino and hydroxy substituents *ortho* or *para* to a CF_3 group. The loss of fluoride ion indicates a considerable loosening of the carbon-fluorine bond which may be represented by resonance and inductive structures (XII and XIII, respectively).



Accordingly, it was found that 3-trifluoromethylphenothiazine (3, 4), which is capable of similar electronic activation, produced (73% yield) the corresponding ortho ester on treatment with methanolic potassium hydroxide. In contrast, the 2- and 4- CF_3 analogs which do not participate in such a mechanism were recovered unchanged.

In this work, the Ullmann method commencing with II was utilized to prepare 4-trifluoromethylphenothiazine which prior to this time was available only as a by-product in the thionation of 3-trifluoromethyldiphenylamine (4-6).

Currently, we are investigating the ortho ester reaction of trifluoromethyl derivatives of other heterocyclic and carbocyclic systems.

EXPERIMENTAL

Melting points were determined with an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York and Microanalysis, Inc., Wilmington, Delaware. IR spectra were recorded on a Perkin-Elmer Model 137 Spectrophotometer. Nmr spectra were taken in deuteriochloroform by Sadtler Research Laboratories, Inc., Philadelphia, Pennsylvania, on a Varian A-60A instrument using tetramethylsilane as internal standard.

2-Bromo-3-nitrobenzotrifluoride (II).

2-Bromo-3-nitrobenzoic acid (21) (49.2 g., 0.2 mole) was placed in a 250 ml. Hastelloy-C pressure vessel which was sealed and cooled in a dry ice-acetone bath. After evacuation to 0.1 mm. pressure, the vessel was charged with sulfur tetrafluoride (22) (76.8 g., 0.71 mole). The reactor was allowed to warm to room temperature overnight and was heated to 140° (2 hours) and at 140-145° for 5 hours under autogeneous pressures.

The cooled pressure vessel was vented and the mixture was treated with 300 ml. of 5% potassium hydroxide. Extraction of the filtered solid with ether and concentration of the ether solution provided 2-bromo-3-nitrobenzotrifluoride (II, 44 g., 82%) as tan crystals, m.p. 57-58°. The analytical sample (white crystals) from methanol melted at 61.5-62°.

Anal. Calcd. for $C_7H_3BrF_3NO_2$: C, 31.13; H, 1.12; N, 5.19. Found: C, 30.98; H, 1.07; N, 5.08.

2'-Amino-2-nitro-6-trifluoromethyldiphenylsulfide (IV).

A solution of 2-bromo-3-nitrobenzotrifluoride (9.86 g., 0.0365 mole) in absolute ethanol (45 ml.) was added to a solution of *o*-aminobenzenethiol (4.56 g., 0.0365 mole), sodium hydroxide (1.5 g., 0.0365 mole), water (11 ml.) and absolute ethanol (82 ml.). The stirred mixture was heated at reflux for 2 hours and on dilution with water (200 ml.) produced IV [8.8 g. (77%), m.p. 110-111°]. Two recrystallizations from aqueous ethanol gave

yellow needles, m.p. 112-113°.

Anal. Calcd. for $C_{13}H_9F_3N_2O_2S$: C, 49.68; H, 2.89; N, 8.92. Found: C, 49.78; H, 2.68; N, 8.64.

2′-Formamido-2-nitro-6-trifluoromethyldiphenylsulfide (VI).

A mixture of 2′-amino-2-nitro-6-trifluoromethyldiphenylsulfide (14.3 g., 0.0455 mole) and 90% formic acid (143 g.) was heated at reflux for 10 hours and poured over crushed ice. Solidification of the gum by scratching and subsequent recrystallization from carbon tetrachloride provided VI as white needles (11.4 g., 73%), m.p. 111-111.5°.

Anal. Calcd. for $C_{14}H_9F_3N_2O_3S$: C, 49.12; H, 2.65; N, 8.19. Found: C, 49.25; H, 2.79; N, 8.09.

2′-Acetamido-2-nitro-6-trifluoromethyldiphenylsulfide (V).

A mixture of IV (2.0 g., 0.006 mole), acetic anhydride (9 ml.) and pyridine (0.5 ml.) was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* to a dark brown paste. Trituration of the latter with ethanol slowly precipitated a yellow solid which on recrystallization from carbon tetrachloride gave V (0.76 g., 34%) as yellow needles, m.p. 122-124° (used in the next step without elemental analysis).

10-Acetyl-1-trifluoromethylphenothiazine (VII).

To a stirred mixture of potassium hydroxide (1.30 g., 0.02 mole) in 95% ethanol (10.5 ml.) and acetone (200 ml.) under nitrogen was added at 25°, 3.56 g. (0.01 mole) of the acetamido derivative (V). The reaction was evaporated on a steam-bath, the tan pasty residue was extracted with ether, and the ether extracts were dried (magnesium sulfate). Concentration provided a pale orange solid, m.p. 91-100°, which on recrystallization from 50% methanol afforded VII as colorless needles (1.7 g., 56%), m.p. 110-111°.

Anal. Calcd. for $C_{15}H_{10}F_3NOS$: C, 58.24; H, 3.26; N, 4.53; S, 10.37. Found: C, 58.27; H, 3.18; N, 4.59; S, 10.13.

1-Trifluoromethylphenothiazine (VIII).

To a stirred solution of the formamido derivative (VI) (27.5 g., 0.08 mole) in acetone (300 ml.) was added under nitrogen 1 *N* ethanolic potassium hydroxide (170 ml.). After refluxing for 2.5 hours the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue on vacuum distillation gave VIII as an orange oil, b.p. (0.5 mm.) 111.5-125° (19 g., 88%). Subsequent distillation provided the analytical sample as a yellow oil, b.p. (0.6 mm.) 113-115°, which solidified after two months, m.p. 28.5-30°. 1-Trifluoromethylphenothiazine gave the usual blood-red color test with nitric acid. IR (natural film): 2.87 (NH), 12.77 (vicinal trisubstituted) and 13.40 μ (*o*-disubstituted).

Anal. Calcd. for $C_{13}H_8F_3NS$: C, 58.42; H, 3.02; N, 5.24; S, 12.00. Found: C, 58.35; H, 2.83; N, 5.11; S, 12.28.

The above product was identical to that obtained in the hydrolysis of VII with 20% hydrochloric acid (reflux, 2 hours).

Acid Hydrolysis of VIII. Phenothiazine-1-carboxylic Acid (IX).

1-Trifluoromethylphenothiazine (VIII, 0.04 g.) and concentrated sulfuric acid (0.6 ml.) were heated at 125° for 50 minutes. The mixture was diluted with water, extracted with ether and the extracts brought to dryness. Recrystallization of the residue from 70% ethanol (carbon) and treatment of the filtrate with sodium dithionite provided on cooling phenothiazine-1-carboxylic acid (IX) (23), m.p. 259° dec. Mixture melting point with an authentic sample (m.p. 264° dec.) gave m.p. 260-262° dec. Infrared spectra were identical.

Basic Hydrolysis of VIII. Trimethyl Orthophenothiazine-1-carboxylate (X).

A mixture of VIII (4 g.), potassium hydroxide (96 g.), water (65 ml.) and methanol (130 ml.) was heated at reflux for 17 hours. The suspension was diluted with water and extracted with ether. Evaporation of the ether extracts and two recrystallizations of the residue from 70% ethanol (carbon) gave trimethyl orthophenothiazine-1-carboxylate (X, 47%) as pearl-white platelets, m.p. 77-78°. IR (nujol mull): 2.98 (NH), 9.2-9.4 (OCH_3, strong and broad), 12.82 (vicinal trisubstituted) and 13.20 μ (*o*-disubstituted); nmr, δ: 3.20 (s, 9H), 6.60-7.25 (m, 6H), 7.42 (s, 1H) and 7.68 (1, NH). Acidification of the reaction filtrate also yielded IX (1.0 g., 27%), m.p. 264° dec.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; S, 10.57. Found: C, 63.14; H, 5.46; N, 4.59; S, 10.78.

Treatment of the ortho ester (X) with glacial acetic acid at room temperature produced an almost quantitative yield of methyl phenothiazine-1-carboxylate (XI), m.p. 114-115° [lit. (21) m.p. 113-113.5°].

The reaction between 3-trifluoromethylphenothiazine and methanolic potassium hydroxide as described above yielded as the only product, trimethyl orthophenothiazine-3-carboxylate (73%), white plates from benzene, m.p. 146.5-147°. IR (nujol mull): 2.99 (NH), 9.2-9.4 (OCH_3, strong and broad), 11.31 and 12.00 (asymmetric trisubstituted) and 13.25 μ (*o*-disubstituted).

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.05; H, 5.45; N, 4.63.

2′-Bromo-2-nitro-6-trifluoromethyldiphenylsulfide (XIV).

To a warm mixture of *o*-bromothiophenol (24) (2.38 g., 0.0126 mole), ethanol (12 ml.), water (1 ml.) and sodium hydroxide (0.52 g., 0.0126 mole) was added a solution of 2-bromo-3-nitrobenzotrifluoride (II) (3.4 g., 0.0126 mole) in ethanol (10 ml.). The reaction mixture was refluxed 2 hours, cooled and filtered. Recrystallization of the product from ethanol provided XIV (80%) as yellow crystals, m.p. 106-106.5°.

Anal. Calcd. for $C_{13}H_7BrF_3NO_2S$: C, 41.29; H, 1.87; N, 3.70. Found: C, 41.66; H, 1.77; N, 3.81.

2-Amino-2′-bromo-6-trifluoromethyldiphenylsulfide (XV).

To a solution of XIV (3.4 g., 0.009 mole) in ethanol (36 ml.) at 45° was added dropwise stannous chloride dihydrate (6.8 g., 0.03 mole) in concentrated hydrochloric acid (15 ml.). The reaction was refluxed for 45 minutes, diluted with water and extracted with ether. The combined extracts were dried, evaporated and the pink residue (XV) (2.65 g., 85%), m.p. 99-101°, was used in the next reaction without elemental analysis (IR bands were as expected).

2′-Bromo-2-formamido-6-trifluoromethyldiphenylsulfide (XVI).

A suspension of XV (2.65 g., 0.0076 mole) in 90% formic acid (30 ml.) was refluxed 5 hours, cooled and filtered. Recrystallization of the product from ethanol gave XVI (93%) as white needles, m.p. 196-197°.

Anal. Calcd. for $C_{14}H_9BrF_3NOS$: C, 44.69; H, 2.41; N, 3.72. Found: C, 44.73; H, 2.45; N, 3.62.

4-Trifluoromethylphenothiazine (XVII).

A stirred mixture of XVI (2.3 g., 0.0061 mole), anhydrous potassium carbonate (1.67 g., 0.0122 mole), copper-bronze powder (0.12 g.) and dimethylformamide (26 ml.) was refluxed 8 hours and filtered. The filtrate was acidified with dilute hydrochloric acid, extracted with ether, the ether was evaporated, and the residue triturated with petroleum ether (20-40°). On cooling,

XVII was obtained as yellow solid (0.8 g., 79%), m.p. 72-73° [lit. (4) m.p. 72-73°]. Mixture melting point with an authentic sample was not depressed and IR spectra were identical.

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