# New Synthesis of Thiphenamil Hydrochloride

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**A new synthesis of thiphenamil hydrochloride, 2-(diethylaminoethyl)diphenylthioacetate hydrochloride, a direct-acting smooth muscle antispasmodic with no appreciable anticholinergic or muscarinic activity, is described. The synthesis is carried out under mild conditions and is much simpler than any other known method of preparing this drug.**

THIPHENAMIL HYDROCHLORIDE [2-(diethylaminoethyl)diphenylthioacetate hydrochloride][1] was prepared in two steps from diphenylacetyl chloride by reacting the latter with ethylene sulfide, followed by treatment of the resulting 2-(chloroethyl)diphenylthioacetate with diethylamine. Ethylene sulfide is not commercially available, but it can be prepared easily from ethylene carbonate and potassium thiocyanate by the method of Searles and Lutz (1). Ethylene sulfide polymerizes readily, so it is advisable to prepare it immediately before use.

## EXPERIMENTAL

**2-(Chloroethyl)diphenylthioacetate.**—A solution of 231 Gm. (1 mole) of diphenylacetyl chloride in 225 ml. of benzene was mixed with 63 Gm. (1.05 moles) of ethylene sulfide in a suitable vessel fitted with an air-tight closure. The air above the surface of the liquid was swept out with nitrogen, the vessel sealed, and the mixture allowed to stand at room temperature for 7 days. At the end of this period the liquid was filtered with decolorizing carbon and the solvent evaporated from the filtrate under reduced pressure below 40°. The yield of white, crystalline product was 270 Gm. (93%) melting at 45°–47°. 2-(Chloroethyl)diphenylthioacetate was originally prepared by this author (2) from potassium diphenylthioacetate and ethylene chlorobromide.

**2-(Diethylaminoethyl)diphenylthioacetate Hydrochloride.**—The 2-(chloroethyl)diphenylthioacetate from the preceding reaction was dissolved in 146 Gm. (2 moles) of diethylamine, and the mixture was allowed to stand in a sealed vessel at room temperature for 7 days. At the end of this period the unreacted diethylamine was removed by evaporation under reduced pressure below 30°. The residual material was stirred with 600 Gm. of cracked ice and water in which 30 Gm. of sodium carbonate had been dissolved. The basic ester precipitated as a white, waxy solid. This was collected on a filter and washed thoroughly with cold water. The pure basic ester melts at 35°, but in this case the product was not purified.

The crude material was suspended in approximately twice its volume of water containing the calculated quantity of hydrogen chloride (77 ml. of hydrochloric acid, sp. gr. 1.19 in 600 ml. of water for 0.93 mole). When all of the base had dissolved the pH of the solution was adjusted to 5.0 with additional hydrochloric acid, or with sodium hydroxide. Five grams of decolorizing carbon was added and the mixture filtered with suction at 60°. The product crystallized as the monohydrate when the filtrate was slowly cooled. The cooling was carried almost to the freezing point and the crystals collected on a filter. The anhydrous salt was obtained by placing the monohydrate in a hot-air drier at 60° and raising the temperature at the rate of 5°/hr. to 105°. The yield of fine, white powder was 244 Gm. (72%) melting at 127°–129°.

## DISCUSSION

This synthesis of thiphenamil hydrochloride precludes the use of high reaction temperatures and to a great extent the use of flammable solvents as well. These are advantages in a manufacturing process. In addition, this procedure offers a considerable saving in labor and materials compared to other known methods for the preparation of this compound.

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[1] Marketed as Trocinate by the Wm. P. Poythress & Co., Richmond, Va.

## REFERENCES

(1) Searles, S., and Lutz, E. F., *J. Am. Chem. Soc.*, **80**, 3168 (1958).

(2) Richardson, A. G., U. S. pat. 2,390,555 (December 11, 1945).