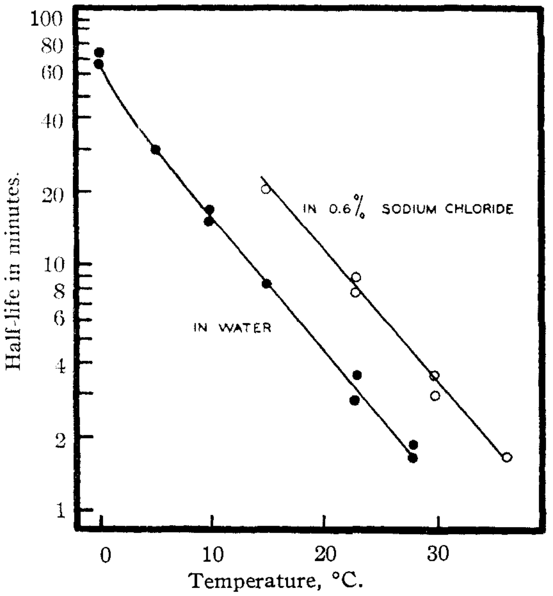

Fig. 1.—Relationship of the half-life of 2-chloro-2′-hydroxydiethyl sulfide to temperature in water and in 0.6% sodium chloride solutions.

Sodium chloride solutions and blood samples were shaken with equal volumes of chloroform which extracted approximately 70% of the Semi-H and avoided introducing interfering chloride ions into the chromogenic reaction mixture. The analytical procedure was then the same as for water except that the reaction mixture was altered to contain 10% chloroform and 45% instead of 55% isopropyl alcohol.

The half-life of Semi-H in heparinized rabbit blood at 25° was found to be 5.8 minutes, and in plasma, 8.2 minutes. The value in 0.6% saline for 25° interpolated from Fig. 1 was 6.5 minutes. Unlike the reaction of H, which is markedly slowed in blood, presumably due to solution and protection in a lipoid phase, the reaction of the more water-soluble Semi-H is not significantly different in blood than in a solution of equivalent salt content.

Summary

A method has been described for the synthetic preparation of 2-chloro-2′-hydroxydiethyl sulfide and for isolation of its condensation products with cysteine and valine. Data are given for the hydrolysis rate of 2-chloro-2′-hydroxydiethyl sulfide at different temperatures in water, 0.6% saline and rabbit blood. Unlike 2,2′-dichloroethyl sulfide, the mono-chloro compound did not persist in blood longer than in equivalent saline.

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[Contribution from the Sterling-Winthrop Research Institute]

Dialkylaminoalkyl Diarylthiolacetates

By R. O. Clinton and U. J. Salvador

The recent appearance of a patent[1] describing several dialkylaminoethyl diphenylthiolacetates prompts a description of similar work carried out in these laboratories, prior to the appearance of this patent.

Diethylaminoethyl diphenythiolacetate hydrochloride was prepared in high yield by the condensation of 2-diethylaminoethanethiol with diphenylacetyl chloride in dry benzene. In a similar manner a number of other dialkylaminoalkyl diphenylthiolacetates were prepared in excellent yield. The substitution of 9-fluorenecarboxyl chloride for the diphenylacetyl chloride effected analogous results, but with some diminution of yield due to side reactions of the acid chloride.

This direct reaction of the thiol with the acid chloride offers evident advantage over the somewhat tedious procedure described by the patent,[1] since the intermediates are readily prepared and a single reaction affords a nearly pure, water-soluble product. In certain cases it has proven advantageous to prepare a salt other than the hydrochloride (*e.g.*, because of hygroscopicity); these salts are readily obtained from the easily prepared bases in this series by conducting the condensation of thiol and acid chloride in a mixture of water, base and inert solvent, as described in the experimental part.

The melting point of the diethylaminoethyl diphenylthiolacetate prepared in the present work differed markedly from that given by the patent[1]; this difference has been shown to be due to diethylamine hydrochloride present as an impurity in the compound when prepared by the patent procedure.

Experimental[2]

2-Diethylaminoethyl Diphenylthiolacetate Hydrochloride.—To a stirred, cooled solution of 13.3 g. of 2-diethylaminoethanethiol[3] in 100 ml. of dry benzene was slowly added a solution of 23.05 g. of pure diphenylacetyl chloride[4] in 200 ml. of dry benzene. A white crystalline precipitate appeared immediately. When addition was complete the mixture was heated to boiling for a few minutes, cooled in ice and diluted with an equal volume of Skellysolve B. Filtration and drying of the precipitate gave 31.3 g. of product, m. p. 125.5–127.5°. One recrystallization from benzene–Skellysolve B yielded tiny white needles, m. p. 129.5–130.5°. The patent[1] reports a melting point of 82–85°.[5]

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(1) U. S. Patent 2,390,555 (Dec. 1945).

(2) All melting points and boiling points are corrected. We are indebted to Mr. Morris Auerbach and staff for the analyses.

(3) Albertson and Clinton, This Journal, **67**, 1222 (1945).

(4) Hellerman, Cohn and Hoen, *ibid.*, **50**, 1725 (1928).

(5) A sample of this compound when prepared by the patent method[1] melted initially at 89–98°. Several crystallizations from benzene-Skellysolve B gave a material melting at 129.5–130.5°; mixed m. p. with the present preparation was 129.5–130.5°. The impurity was shown by isolation and mixed m. p. determination to be diethylamine hydrochloride.

Anal. Calcd. for $C_{20}H_{25}NOS{\cdot}HCl$: C, 66.01; H, 7.20; N, 3.84. Found: C, 66.19; H, 7.01; N, 3.69.

In a similar fashion there were prepared:

3-N-Piperidinopropyl diphenylthiolacetate hydrochloride, from diphenylacetyl chloride and 3-N-piperidinopropanethiol,[6] white prisms from absolute alcohol–ethyl acetate, m. p. 155.5–157.0°.

Anal. Calcd. for $C_{22}H_{27}NOS{\cdot}HCl$: Cl, 9.09; S, 8.22. Found: Cl, 9.09; S, 8.18.

3-Diethylaminopropyl diphenylthiolacetate hydrochloride, from diphenylacetyl chloride and 3-diethylaminopropanethiol,[6] rosets of white needles from absolute alcohol–ethyl acetate, m. p. 128.5–129.5°.

Anal. Calcd. for $C_{21}H_{27}NOS{\cdot}HCl$: Cl, 9.38; S, 8.48. Found: Cl, 9.65; S, 8.69.

2-Diethylaminoethyl fluorene-9-thiolcarboxylate hydrochloride, from fluorene-9-carboxyl chloride[7] and 2-diethylaminoethanethiol, white prisms from absolute alcohol–ethyl acetate, m. p. 208–210° (dec.).

Anal. Calcd. for $C_{20}H_{23}NOS{\cdot}HCl$: Cl, 9.80; S, 8.86. Found: Cl, 9.73; S, 8.77.

4-Chloro-N,N-diethylamylamine Hydrochloride.—A solution of 477 g. of redistilled 4-diethylamino-2-pentanol (b. p. 95–96° at 8 mm.) in 1200 ml. of dry chloroform was treated at −5 to −10° with mechanical stirring with a solution of 369 g. of purified thionyl chloride in 500 ml. of dry chloroform, added during forty-five minutes. When the addition was complete the cold bath was removed and the clear yellow-orange mixture allowed to warm to room temperature (three hours). The solvent and excess thionyl chloride were removed *in vacuo;* the residue crystallized readily on standing. The crude yield was *ca.* 640 g., m. p. 89–91°. A portion crystallized from ethyl acetate with decolorization (Darco G-60) formed white leaflets, m. p. 98°.[8]

Anal. Calcd. for $C_9H_{20}ClN{\cdot}HCl$: C, 50.47; H, 9.88; N, 6.54. Found: C, 50.65; H, 9.64; N, 6.46.

5-Diethylamino-2-pentanethiol.—A solution of 590 g. of 4-chloro-N,N-diethylamylamine hydrochloride and 210 g. of thiourea in 1500 ml. of absolute alcohol was refluxed for eighteen hours. The alcohol was removed *in vacuo;* the residue partially crystallized on cooling. A sample of this crystalline material when repeatedly crystallized from absolute alcohol–ethyl acetate had a constant m. p. of 142–143°; analyses indicated it to be a salt of 5-diethylamino-2-pentylisothiouronium chloride hydrochloride with two molecules of thiourea.[9]

Anal. Calcd. for $C_{10}H_{25}Cl_2N_3S{\cdot}2NH_2CSNH_2$: C, 32.57; H, 7.51, N, 22.16; S, 21.74. Found: C, 32.77; H, 7.53; N, 21.69; S, 21.81.

Hydrolysis of the above crude partially crystalline residue with a two mole proportion of aqueous sodium hydroxide in the usual way followed by extraction and distillation gave 246 g. (50.9%) of thiol, b. p. 80–87° at 7–8 mm. The pure thiol had b. p. 94.0° at 11.0 mm., n^{25}_{D} 1.4630.

Anal. Calcd. for $C_9H_{21}NS$: N, 7.99. Found: N, 7.88.

The **picrate** formed long, stout, canary-yellow needles from alcohol, m. p. 62–65°.

Anal. Calcd. for $C_{15}H_{24}N_4O_7S$: S, 7.93, Found: S, 7.81.

The ***p*-nitrothiolbenzoate hydrochloride** formed tiny pale yellow needles from absolute alcohol–ethyl acetate, m. p. 146–147°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3S{\cdot}HCl$: S, 8.88; Cl, 9.82. Found: S, 8.85; Cl, 9.82.

5-Diethylamino-2-pentyl Diphenylthiolacetate Hydrochloride.—This compound was prepared by the above-described general method. It formed small, white, very hygroscopic needles from benzene–Skellysolve A, m. p. 66–68°.

Anal. Calcd. for $C_{23}H_{31}NOS{\cdot}HCl$: Cl, 8.73; S, 7.90. Found: Cl, 8.74; S, 7.58.

The base was obtained as an oil, b. p. 130–135° at 0.2–0.4 mm., by treatment of a water–chloroform mixture of equimolecular amounts of thiol and sodium bicarbonate with a chloroform solution of the acid chloride at 0°, followed by separation of the chloroform layer and evaporation to dryness. A crystalline non-hygroscopic **citrate** was readily obtained by treatment of an absolute alcohol solution of the base with an equivalent amount of citric acid monohydrate: rosets of small white needles from absolute alcohol–ethyl acetate, m. p. 86–87° with gas evolution.

Anal. Calcd. for $C_{23}H_{31}NOS{\cdot}C_6H_8O_7$: N, 2.49. Found: N, 2.36.

Summary

There are described a number of dialkylaminoalkyl diarylthiolacetate salts and certain intermediates required in their preparation.

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(6) Laskowski and Clinton, submitted for publication in THIS JOURNAL.

(7) Vorländer and Pritzsche, *Ber.*, **46**, 1794 (1913).

(8) Clemo and Hook, *J. Chem. Soc.*, 608 (1936), reported failure to obtain a crystalline hydrochloride by this method. Hass and Huffman, THIS JOURNAL, **63**, 1233 (1941), prepared the compound in 11.7% over-all yield from 1-chloropentane. They reported a melting point of 99°.

(9) Thiourea apparently promoted cyclization of 4-chloro-N,N-diethylamylamine hydrochloride to 1,1-diethyl-2-methylpyrrolidinium chloride. A similar phenomenon has not been observed previously in this type of thiol synthesis; *cf.* however Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).