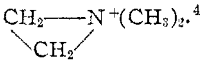
[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

β-Dimethylaminoethyl Esters of Organic Dithio Acids. I. Dithioacetylcholine Iodide

BY R. W. BOST AND OTIS L. SHEALY[1]

The dialkylamino-alkyl esters of organic acids have been studied extensively because of their interesting physiological properties. In the aliphatic series esters of the type R-COO-$(CH_2)_n$-NR′R″ often show marked parasympathomimetic action when used as quaternary hydroxides or quaternary halides. Hunt and Taveau[2] noted in 1906 that acetylcholine, CH_3-COO-CH_2-CH_2-N-$(CH_3)_3OH$ produced a distinct, though brief, muscarinic action. Since then numerous modifications of the acetylcholine-type molecule have been made with the purpose of relating structure to pharmacological activity. Structural variations have included the use of different alkyl (and aryl) groups for R, R′ and R″; the variation of the length of the chain between the ester and the amino groupings; the introduction of substituents into the chain; and the substitution of sulfur, phosphorus, arsenic and antimony for the nitrogen in the quaternary amino group.

Studies of the effect of substituting sulfur for oxygen in the ester linkage are incomplete. Renshaw, *et al.*,[3] synthesized thiolacetylcholine iodine, CH_3-CO-S-CH_2-CH_2-$N(CH_3)_3I$ and its β-methyl analog. These compounds possessed less muscarinic activity than acetylcholine but showed increased nicotinic and curariform effects. The preparation of acetylcholine analogs in which both oxygens of the ester grouping are replaced by sulfur has not been reported.

A successful synthesis of dithioacetylcholine iodide, CH_3-CS-S-CH_2-CH_2-$N(CH_3)_3I$, was developed by the authors in the course of a study of aliphatic and aromatic dithio acids. The β-dimethylaminoethyl ester of dithioacetic acid was prepared by treating sodium dithioacetate with β-chloroethyl dimethylamine in aqueous solution. The dithio ester separated in high yield as an insoluble red oil. Presumably the reaction involved attack of the nucleophilic CH_3-CSS- ion on an intermediate ethyleneimonium ion,  CH_2——$N^+(CH_3)_2$ ($\backslash CH_2/$).[4] The esterification reaction took precedence over the dimeric quaternization of the amine, which normally goes to virtual completion in two to three hours in water solution.[5]

The dithio ester was purified by an extraction procedure, and the hydrochloride and the methiodide were prepared from solutions of the ester in anhydrous benzene. Both the hydrochloride and the methiodide showed reactions typical of compounds containing thion sulfur. Thus, aqueous silver nitrate gave an immediate black precipitate of silver sulfide. Both compounds were readily decomposed by mild oxidizing agents (3% hydrogen peroxide or 3 *N* nitric acid). Absorption spectra studies indicated a rapid decomposition of dilute aqueous solutions of the hydrochloride and the methiodide; after one week a typical absorption band in the ultraviolet attributed to the dithio ester grouping had completely disappeared.

A pure sample of dithioacetylcholine iodide has been submitted to the Wm. S. Merrell Co. for pharmacological study. Results will be reported in a future paper. Absorption spectra of dithioacetylcholine iodide and related compounds will be reported in subsequent papers of this series.

Experimental

Sodium Dithioacetate.—The method of Houben and Pohl[6] was used. An ether solution of CH_3-CS-S-Mg-I was prepared from 200 g. (1.41 mole) of methyl iodide as outlined in the reference. After standing in melting ice for 24 hours, the cold ethereal solution was cautiously treated first with ice and then with ice-cold dilute hydrochloric acid. The red-brown ether layer was separated, washed with cold water, and extracted with 100-ml. portions of 1.25 *N* NaOH. The first three extractions gave a light yellowish-red solution. Subsequent extracts, which were dark red-black, were discarded. The solution of the sodium salt obtained in the first three extractions was covered with ether, and the free acid was liberated by adding cold dilute hydrochloric acid. The ether solution of dithioacetic acid was again washed with cold water and extracted with 100-ml. portions of 1.25 *N* NaOH. The liberation of the acid and extraction with sodium hydroxide was repeated a third time. In the final extraction 300 ml. of 1.25 *N* NaOH was used. The solution of the sodium salt was back-titrated with 1.50 *N* HCl until free dithioacetic acid just began to separate. Seventeen ml. of hydrochloric acid was required for back-titration; yield of sodium dithioacetate, 0.35 mole (25%). The solution of sodium dithioacetate was washed twice with 100-ml. portions of ether and stored in a tightly stoppered flask. Only slight decomposition was evident after storage for a month at room temperature.

p-Bromophenacyl Ester of Dithioacetic Acid.—The sodium dithioacetate prepared was characterized by the formation of the solid *p*-bromophenacyl ester. Two and eight-tenths grams of *p*-bromophenacyl bromide was dissolved in 25 ml. of hot 95% ethyl alcohol, and 0.01 mole of neutral sodium dithioacetate in 10 ml. of water was added slowly with stirring. The mixture was boiled gently for 10 minutes and allowed to cool to room temperature. The yellow precipitate was separated, dried and recrystallized once from absolute ethyl alcohol. The ester was obtained as yellow plates melting at 96.5–97.0°.

Anal. Calcd. for $C_{10}H_9BrOS_2$: S, 22.17. Found: S, 22.27.

β-Chloroethyldimethylamine.—An adaptation of the method of Slotta and Behnisch[7] was used. Two hundred grams (1.68 moles) of thionyl chloride and 100 g. (1.12 mole) of β-dimethylaminoethanol were refluxed for 3 hours in 400 ml. of benzene. The reaction mixture was then cooled and the supernatant benzene was filtered off (filter stick). The crude solid hydrochloride was dissolved in a minimum volume of water and a large excess of cold 30% sodium hydroxide was added. The β-chloroethyldimethylamine was extracted with four 250-ml. portions of ether. The ether extracts were combined and dried over anhydrous potassium carbonate for three hours. The volume of the ether solution was reduced to about 300 ml., and the resulting solution was fractionated; yield 59 g. (49%) of β-chloroethyldimethylamine, b.p. 107–109° at 760 mm.

β-Dimethylaminoethyl Ester of Dithioacetic Acid.—Twelve grams (0.11 mole) of freshly distilled β-chloroethyl-

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[1] 1949–1950 du Pont Fellow in Chemistry.

[2] Hunt and Taveau, *Brit. Med. J.*, **2**, 1788 (1906).

[3] Renshaw, *et al.*, THIS JOURNAL, **60**, 1765 (1938).

[4] Bartlett, Ross and Swain, *ibid.*, **69**, 2971 (1947).

[5] Knorr, *Ber.*, **37**, 3506 (1904).

[6] Houben and Pohl, *ibid.*, **40**, 1303 (1907).

[7] Slotta and Behnisch, *ibid.*, **68B**, 754 (1935).

dimethylamine was added to 0.1 mole of sodium dithioacetate in about 150 ml. of water. The solution was stirred gently at room temperature for 3 hours. The amino ester separated as a red oil; at the end of 3 hours the color of the sodium dithioacetate had been almost completely discharged. The ester was taken up in benzene and then extracted from the benzene solution with 20-ml. portions of 5% hydrochloric acid. A slight excess of 5% sodium hydroxide was added to the aqueous solution of the ester hydrochloride, and the free ester was again extracted with benzene. The benzene solution was dried for 3 hours over anhydrous potassium carbonate and used in the preparation of the hydrochloride and the methiodide.

β-Dithioacetoxyethyldimethylammonium Chloride.—Cylinder hydrogen chloride was passed through concentrated sulfuric acid and a spray trap, and then bubbled into the dry benzene solution of the β-dimethylaminoethyl ester prepared from 0.1 mole of sodium dithioacetate. The hydrochloride precipitated as an amorphous yellow solid. Passage of hydrogen chloride through the solution was continued until the supernatant benzene was practically colorless. A yield of 15.2 g. of the hydrochloride (76%, calcd. from the sodium salt) was obtained. The hydrochloride was recrystallized twice from chlorobenzene as hygroscopic yellow plates melting at 130–132°.

Anal. Calcd. for $C_6H_{14}ClNS_2$: N, 7.01; S, 32.10. Found: N, 6.80; S, 32.35.

β-Dithioacetoxyethyltrimethylammonium Iodide (Dithioacetylcholine Iodide).—Eighty-five grams (0.6 mole) of methyl iodide was added to the dry benzene solution of the β-dimethylaminoethyl ester prepared from 0.1 mole of sodium dithioacetate. The mixture was allowed to stand for three days at room temperature. The methiodide precipitated as an amorphous greenish-yellow solid which was analyzed without recrystallization. A yield of 22.0 g. (72% from the sodium salt) was obtained; m.p. 172.5–173.5° (dec.), solubility in water 3.3 g. per 100 ml. at 28°.

Anal. Calcd. for $C_7H_{16}INS_2$: N, 4.59; S, 21.01. Found: N, 4.56; S, 21.00.

Summary

1. β-Dithioacetoxyethyldimethylammonium chloride and β-dithioacetoxyethyltrimethylammonium iodide (dithioacetylcholine iodide) have been prepared.

2. A new derivative, the *p*-bromophenacyl ester, of dithioacetic acid has been prepared.

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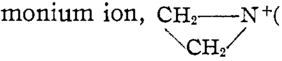
β-Dimethylaminoethyl Esters of Organic Dithio Acids. II. Esters of Aromatic Dithio Acids

BY R. W. BOST AND OTIS L. SHEALY[1]

The previous paper in this series[2] described a synthesis of the β-dimethylaminoethyl ester of dithioacetic acid. The analogous esters of a series of eleven aromatic dithio acids have now been prepared. Synthesis of these esters was accomplished by treating zinc or sodium salts of the acids with β-chloroethyldimethylamine.

With the exception of 4-methyldithiobenzoic acid, which was obtained by the action of carbon disulfide on *p*-tolylmagnesium bromide, the aromatic dithio acids were prepared by a modification of the method of Levi and Bruni.[3] Aromatic aldehydes, dissolved or suspended in alcohol, were heated with ammonium polysulfide of the approximate composition $(NH_4)_2S_2$. Acidification of the colored supernatant liquid gave "dithio acids."[3] However, it was found that yields of acid, in some cases the major part of the product, could also be obtained from the resinous material which precipitated on heating the aldehyde–ammonium polysulfide mixture. Digestion of this resinous material with saturated alcoholic potassium hydroxide, followed by acidification, gave an acid identical in all respects with that obtained from the supernatant liquid. In view of the well-known susceptibility of the dithio acids to oxidation by atmospheric oxygen, no attempt was made to isolate and purify the free acids. Instead, the acids were isolated as their sodium and zinc salts. The sodium salts were characterized by the formation of S-benzylpseudothiuronium salts or *p*-bromophenacyl esters.

In the initial work β-dimethylaminoethyl esters were synthesized by refluxing β-chloroethyldimethylamine with zinc salts of the acids in anhydrous organic solvents. The zinc chloride was filtered from the reaction mixture, and the highly colored solution of the ester was used directly in the formation of derivatives. Though this method was successful with dithiobenzoic, 4-methydithiobenzoic and 4-methoxydithiobenzoic acids, wider application was hindered by difficulty in finding suitable solvents for the zinc salts.

A more satisfactory synthesis of the esters involved reaction of sodium salts of the acids with β-chloroethyldimethylamine in aqueous solution. The reaction was carried out at room temperature; the dithio esters separated as water insoluble colored oils which were converted into hydrochlorides and methiodides. Formation of the esters in water solution probably involved the attack of the nucleophilic $ArCSS^-$ ion on an intermediate ethyleneimonium ion,  $\underbrace{CH_2 — N^+(CH_3)_2}_{CH_2}$. Bartlett, *et al.*,[4] have shown that the ethyleneimonium ion is an intermediate in cyclization and replacement reactions of β-halogenated trialkylamines. In this case the attack of the $ArCSS^-$ ion takes precedence over the dimeric quaternization of the amine, which normally goes to virtual completion in two to three hours in water solution.[5]

The dithio ester derivatives, such as hydrochlorides, citrates and methiodides, showed reactions typical of compounds containing thion sulfur. Addition of aqueous silver nitrate to the water solutions gave an immediate precipitate of silver sulfide. The derivatives were readily oxidized by 3% hydrogen peroxide or 3 *N* nitric acid;

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[1] du Pont Fellow in Chemistry, 1949–1950.

[2] Bost and Shealy, THIS JOURNAL, **73**, 24 (1951).

[3] Levi and Bruni, *Atti. Accad. Lincei*, **32**, i, 5 (1923).

[4] Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947).

[5] Knorr, *Ber.*, **37**, 3506 (1904).