[CONTRIBUTION FROM THE PHARMACOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY.]

ON SOME METALLIC DERIVATIVES OF ETHYL THIOGLYCOLLATE.[1]

BY CHAS. A. ROUILLER.

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Eight years ago, in a paper published with Rowntree, Abel[2] describes the interesting discovery which he made, that thioglycollic ester dissolves metallic oxides with the greatest ease, with elimination of water and substitution of the hydrogen of the mercaptan grouping by the metal. Thus, 6 molecules of the ester dissolve one molecule of antimony trioxide, forming triethyl-antimony-trithioglycollate, according to the equation

$$Sb_2O_3 + 6HSCH_2CO_2C_2H_5 = 2Sb(SCH_2CO_2C_2H_5)_3 + 3H_2O.$$

The antimony ester compound is an oil insoluble in water, but when treated in absolute alcohol with ammonia yields the corresponding triamide $Sb(SCH_2CONH_2)_3$, which is soluble in water in all proportions with neutral reaction and which, as shown by the numerous experiments of Rowntree, is a powerful trypanosomicidal substance.

Abel also found that mercuric oxide reacts with ethyl thioglycollate even more readily than does antimony trioxide but as the substance obtained by treating the resulting product with ammonia was difficultly soluble in water he did not further investigate the mercury derivatives.

As far as the writer is aware, only two metallic derivatives of thioglycollic ester had been described before the publication of Abel's paper. Wislicenus[3] found that mercuric chloride precipitates from an alcoholic solution of the ester, a voluminous substance which slowly becomes crystalline and separates from boiling alcohol in needles of the composition $ClHgSCH_2CO_2C_2H_5$: if an equimolecular proportion of thioglycollic ester in alcohol is poured upon these crystals they immediately dissolve and on adding much water to the solution a colorless oil, which soon solidifies, is precipitated. When dissolved in a little warm ether, the new compound diethyl-mercury-dithioglycollate, $Hg(SCH_2CO_2C_2H_5)_2$, separates on cooling in long, very slender, silky needles which melt at 56.5°.

Claesson[4] reports that when an alcoholic solution of ethyl thioglycollate is treated with the theoretical amount of sodium ethylate and concentrated somewhat an amorphous precipitate is formed which he assumed to have the structure $NaSCH_2CO_2C_2H_5$ because, when treated with ethyl iodide, it yielded the compound $C_2H_5SCH_2CO_2C_2H_5$.

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[1] A brief summary of this paper has been submitted for publication in the *Proceedings of the National Academy of Sciences.*

[2] Rowntree and Abel, *J. Pharmacol.*, **2**, 108 (1910).

[3] Wislicenus, *Ann.*, **146**, 148 (1868).

[4] Claesson, *Ibid.*, **187**, 113 (1877).

At the suggestion of Professor Abel the writer has investigated the action of a number of metallic oxides on ethyl thioglycollate in the hope of obtaining bactericidal substances, either very slightly soluble which might be used in powder form on wound surfaces or soluble derivatives to be used in solution. The oxides of bismuth, mercury, copper, silver, zinc, tin and arsenic have been tried and all have been found to react energetically with the ester. As the investigation will have to be discontinued for an indefinite length of time it has been thought best to publish in their present incomplete form the results thus far obtained.

Experimental.

The thioglycollic acid was prepared by the method of Friedländer and Chwala[1] except that, as suggested by Holmberg and Mattison,[2] small, thin pieces of zinc, prepared by allowing fused zinc to drop on a cold clay plate, were used instead of zinc dust for the reduction of the dithio acid. The acid was esterified according to the directions of Claesson.[3]

Triethyl-bismuth-trithioglycollate, $Bi(SCH_2CO_2C_2H_5)_3$.—Bismuth trioxide (5.6 g.), prepared by ignition of the subnitrate, was added to 8.7 g. ethyl thioglycollate on the water bath in small portions, with continuous stirring. The liquid at once became lemon-yellow. The oxide, after each addition, fell to the bottom in the form of a sticky mass which, as it was stirred, changed to a thin, colorless, or faintly yellow, gritty coating on the sides of the vessel; as the addition of oxide, stirring and warming were continued, this coating lost its gritty character, became amorphous, detached itself from the sides of the vessel and rolled under the warm liquid like a thick emulsion apparently very much less in amount than the oxide which had been added. The heating was continued for some time under an air condenser; the liquid became deep orange-yellow and the undissolved material did not seem to diminish. On cooling, a white milky layer formed on top; as the cooling continued while the mixture was stirred it changed to a lemon-yellow viscous suspension of solid white globules in a thick, yellow oil. Ten cc. of absolute alcohol was added and the mixture was gently warmed on the water bath. A heavy, nearly white powder settled to the bottom and the clear lemon-yellow supernatant liquid was pipetted off and filtered through a small paper. The insoluble powder was then boiled with 2 cc. of alcohol and the hot liquid used to wash the filter paper.

The yellow alcoholic solution was seeded with crystals obtained in an earlier experiment and set aside in the dark. It soon became turbid and after 48 hours a clear, yellow oil had separated which after a few days had changed to beautiful, small, yellow crystals. These did not change

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[1] Friedländer and Chwala, *Monatsh.*, **28**, 250 (1907).

[2] Holmberg and Mattison, *Ann.*, 353, 124 (1907).

[3] Claesson, *Ibid.*, 187, 113 (1877).

in appearance nor, apparently, in amount after several weeks. The supernatant liquid was finally pipetted off and the crystals were washed with cold absolute alcohol and dried *in vacuo*. Yield, 1.45 g. Attempts to obtain a second crop of crystals by concentration of the mother liquor led only to the deposition of a red-brown varnish on the bottom and sides of the flask.

The crystals melted at 87–88° to a yellow liquid; when heated on platinum they carbonized and then burned to a white ash which turned yellow on further heating.

I. 0.1295 g. substance ignited with 1 cc. concentrated HNO_3 gave 0.0624 g. ash ($Bi_2O_3.SO_3$).

II. 0.2220 g. substance ignited with 1 cc. concentrated H_2SO_4 gave 0.1078 g. ash ($Bi_2O_3.SO_3$).

III. 0.1687 g. substance gave 0.0755 g. Bi_2S_3.

Calc. for $Bi(SCH_2CO_2C_2H_5)_3$: Bi, 36.79. Found: I, 36.84; II, 37.13; III, 36.35.

The ash obtained in analyses (I) and (II) melted over the blast lamp to a mass which was dark yellow when hot and became pale yellow to violet on cooling and slowly lost weight on long ignition, owing to loss of sulfur trioxide. An attempt was made to determine the bismuth as the trioxide by igniting the substance alone, *i. e.*, without nitric or sulfuric acid, but although the odor of sulfur dioxide was plainly perceptible during the ignition the sulfur was evidently not burned off completely as the ash from 0.1036 g. of the compound weighed 0.0460 g. while the weight calculated for Bi_2O_3 is only 0.0425 g.

Diethyl-mercury-dithioglycollate, $Hg(SCH_2CO_2C_2H_5)_2$. — The yellow precipitated mercuric oxide dissolved readily in the ester; the product was treated with a little 75% alcohol and filtered, and much ether was added to the solution. No precipitate was formed but when the solution was concentrated to a very small volume beautiful, long needles separated on cooling. These were washed with cold ether and dried *in vacuo*. The needles melted at 55° and showed all the properties of the compound described by Wislicenus.

Subs., 0.3240; HgS, 0.1704 (Carius). Subs., 0.1694; $BaSO_4$, 0.1775 (Carius).

Calc. for $Hg(SCH_2CO_2C_2H_5)_2$: Hg, 45.71; S, 14.61. Found: Hg, 45.35; S, 14.39.

Ethyl-silver-thioglycollate, $AgSCH_2CO_2C_2H_5$.—The silver oxide was prepared by treating silver nitrate with sodium hydroxide, washing the precipitate with water until the wash water was neutral to litmus paper, then with alcohol and ether, and drying *in vacuo*.

Each small portion of the oxide added to the ester produces a hissing noise with evolution of white fumes, and liberation of some heat. The final product is a black mass of tarry consistency when warm but quite hard when cold. Attempts to purify this by crystallization from alcohol or acetone gave brown suspensions which could not be cleared by repeated filtration; pyridine gave a rather dark but clear brown-yellow solution which on slow evaporation over sulfuric acid yielded a yellow varnish without any indication of crystalline structure.

In another experiment the thioglycollic ester was diluted with about 6 volumes of cold alcohol before adding the oxide; in this case the oxide produced no hissing noise as it fell into the liquid but balled up to a sticky, black mass which on long rubbing changed into silky yellow particles. As the addition of the oxide continued the mixture became thicker and thicker and at the end of the reaction formed a thick, mustard-like mass in which small lumps and streaks of black tar persisted even after very long rubbing. The alcoholic suspension was diluted with acetone and warmed on the water bath whereupon the solid clumped to a sticky, black tar and the liquid assumed a yellow color. By repeatedly boiling with fresh portions of acetone the tar was brought almost completely into solution. The hot acetone solution at once became milky when removed from the water bath but if allowed to cool very slowly deposited fine, yellow needles melting at 75–77°.

The analysis of this substance offered unexpected difficulties and owing to lack of time and material satisfactory results have not yet been obtained. In attempts to analyze it by the Carius method the tubes burst before the substance could be completely decomposed.

I. 0.1307 g. substance heated in a Jena test-tube with concentrated H_2SO_4 and K_2SO_4 and finally a little KNO_3 until the solution was colorless, then diluted with water and precipitated with HCl, gave 0.0826 g. AgCl.

II. 0.1244 g. substance, repeatedly evaporated to dryness with concentrated HNO_3, left a residue insoluble in dilute HNO_3; the filtrate from this gave 0.0734 g. AgCl.

III. 0.2366 g. substance ignited in a crucible left 0.1192 g. silvery residue which, however, did not completely dissolve after several evaporations with HNO_3 or when heated with concentrated H_2SO_4 and then boiled with HNO_3.

Calc. for $AgSCH_2CO_2C_2H_5$: Ag, 47.52. Found: I, 47.56; II, 45.44; III, 50.38.

Of these analyses only (I) can be accepted as having any value for only in this case was a perfect solution obtained, but the results of the other two tend to confirm the correctness of the first; in (II) there remained an insoluble residue which was filtered off before precipitating the silver chloride and the result is therefore probably low, while in (III) the residue of metallic silver which was weighed contained an impurity insoluble in nitric acid and the result would be expected to be high.

Silver carbonate reacted with thioglycollic ester like the oxide, but not quite so vigorously.

When a saturated alcoholic solution of 2.4 g. silver nitrate was slowly treated with 1.4 g. thioglycollic ester a dense precipitate was formed; this dried *in vacuo* to a hard, yellow mass which could be easily powdered and weighed 2.95 g. It gradually turned brown when exposed to the air.

In another experiment, to 1.74 g. of the ester in 300 cc. acetone was slowly added 2.45 g. silver nitrate in 50 cc. acetone and 5 cc. water; there was at once formed a yellow, flocculent precipitate which turned white as the addition of the silver nitrate continued. When dry it formed a very light yellow powder (3.19 g.) which did not appreciably dissolve in acetone, differing in this respect from the product obtained from the ester and silver oxide. It did dissolve readily in hot pyridine and when the hot solution was treated with hot water or acetone and cooled, beautiful pearly scales separated; the pyridine-acetone mixture proved to be the better solvent as the crystals obtained from it could be filtered and washed with great ease while those obtained from aqueous pyridine clogged the filter. The product so obtained did not become appreciably colored when kept in a darkened desiccator.

Cupric Hydroxide and Ethyl Thioglycollate.—The cupric hydroxide was prepared by treating copper sulfate with sodium hydroxide, washing the precipitate free from sulfates by centrifugation, first with water and then with alcohol, and drying *in vacuo.*

The oxide dissolves with great ease in the ester, forming a colorless syrup which gradually becomes thicker and thicker until at the end it has the consistency of very thick molasses. This dissolves in warm 75% alcohol and on slow cooling minute crystals separate which are washed with 75% alcohol and dried *in vacuo.*

I. 0.2345 g. substance ignited with HgO, then dissolved in HCl and precipitated with Zn, gave 0.0218 g. Cu.

II. 0.3267 g. substance ignited with H_2SO_4, then dissolved in HCl and precipitated with Zn, gave 0.0303 g. Cu.

Calc. for $Cu(SCH_2CO_2C_2H_5)_2$: Cu, 21.06. Found: 9.29, 9.27.

An attempt was made to carry out a Carius determination on this substance but even after three days' heating at 200–270° it was apparently not completely decomposed.

As shown by the figures above the compound contains less than $^1/_2$ the amount of copper calculated for the normal derivative $Cu(SCH_2CO_2C_2H_5)_2$, and no simple formula for a substance with 9.3% of copper can be derived; a compound, $HOCuSCH_2CO_2C_2H_5.4HSCH_2CO_2C_2H_5$, would contain 9.35% of copper.

The substances obtained with the oxides of zinc, arsenic and tin have not yet been analyzed and their preparation will therefore not be described at present.

BALTIMORE, MARYLAND.