(8) Reddish, *J. Lab. Clin. Med.*, 14 (1928), 859.
(9) Macht and Reddish, *Proc. Soc. Exptl. Biol. Med.*, 25 (1928), 299.
(10) Macht and Harden, *J. Pharmacol. & Exper. Therap.*, 32 (1928), 321.
(11) Macht, *Proc. Soc. Exptl. Biol. & Med.*, 28 (1931), 687.
(12) Macht and Bloom, *Arch. intern. pharmacodynamie et thérapie*, 25 (1930), 379.
(13) Macht and Kubota, *J. Pharmacol. & Exper. Therap.*, 13 (1919), 31.
(14) Macht and Livingston, *J. Gen. Physiol.*, 4 (1922), 573.
(15) Wood and Loomis, *Philosophical Magazine*, 4 (1927), 417.
(16) Harvey and Loomis, *Nature*, 121 (April 21, 1928), 622.
(17) Schmitt, Olson and Johnson, *Proc. Soc. Exptl. Biol. and Med.*, 25 (1928), 718.
(18) Hsien Wu and Szu-Chih Liu, *Ibid.*, 28 (1931), 782.
(19) Richards and Loomis, *J. Am. Chem. Soc.*, 49 (1927), 3086.

STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. IV. BISMUTH COMPOUNDS OF THIOGLYCOLLIC ACID.*

BY W. M. LAUTER, A. E. JURIST AND W. G. CHRISTIANSEN.

Very little information is available in the literature concerning the toxicity and absorption of sodium bismuth thioglycollates. Harden and Dunning (1) have described the preparation of bismuth thioglycollamide but no data has been published on its toxicity and absorption. A little clinical data is available concerning a market preparation of sodium bismuth thioglycollate but no detailed comparison of the biological characteristics of this and other bismuth compounds has been made. It was the purpose of this investigation to compare bismuth thioglycollates and other bismuth compounds already discussed in previous publications as to their relative toxicity and absorption, as well as to describe their preparation.

Three bismuth derivatives of thioglycollic acid have been prepared: (1) Sodium Bismuth Thioglycollate; (2) Ethyl Thioglycollate; and (3) Bismuth Thioglycollate Triamide.

Of the three bismuth compounds prepared, only two were subjected to biological tests. Both of these were examined as regards their toxicity and absorption in the same manner as those previously discussed. They were injected intramuscularly into albino rats. The absorption was studied by determining quantitatively the unabsorbed bismuth still remaining at the site of injection while the toxicity was estimated from the growth curves of the rats injected. The results obtained are given in the following table. Owing to the slight solubility of bismutho thioglycollamide in water it was necessary to inject it in glycerin solution.

Compound Injected.	Medium for Injection.	Dosage Injected— Mg. Bi/Kg. Body Weight.	Approximate Maximum Tolerated Dose— Mg./Kg. Body Weight.	Per Cent Absorption.
Sodium bismuth thioglycollate	Water	15	Less than 30	38% in 27 days
Bismuth thioglycollamide	Glycerin	50	Less than 50	82% in 3 hours

These two compounds are both more toxic than the bismuth compounds of the fatty acids, the bismuth tartrates, and the iodobismuthates of quinine and

* Scientific Section, A. PH. A., Toronto meeting, 1932.

procaine. They are, however, of the same order of toxicity. They are widely different in absorption since the bismuth thioglycollamide was 82% absorbed in three hours whereas sodium bismuth thioglycollate was only 38% absorbed in twenty-seven days. This latter is unusual in view of the fact that the water-soluble bismuth compounds are usually very rapidly and completely absorbed. Thus, the water-soluble bismuth tartrates are almost completely absorbed in seventy hours. The only basis on which this can be explained is that the sodium bismuth thioglycollate is decomposed into an insoluble bismuth compound when injected which is no more readily absorbed than the bismuth salts of the fatty acids.

From these results there is some evidence that sodium bismuth thioglycollate should give uncertain therapeutic results but the thioglycollamide might, because of its rapid absorption, give more reliable results.

EXPERIMENTAL PART.

Preparation of Sodium Bismuth Thioglycollate.—8.1 Gm. of thioglycollic acid were dissolved in 100 cc. of water and neutralized with sodium carbonate. Then 11.5 Gm. of bismuth hydroxide were added and the whole was boiled until the bismuth hydroxide was dissolved. The solution was clarified and evaporated until an oil separated out. This oil was washed with three volumes of alcohol repeatedly until a solid was obtained. The solid was then washed with ether and dried. The yellow powder was readily water soluble.

Calculated for $(NaCO_2CH_2S)_2BiOH$: Bi—46.2%; S—14.2 %; Na—10.17%.
Found: Bi—42.9%; S—14.42%; Na— 9.0 %.

Preparation of Ethyl Thioglycollate.—50 Gm. of thioglycollic acid were mixed with 50 Gm. of absolute alcohol and 3 cc. of concentrated sulphuric acid. After boiling for two and one-half hours under a reflux an oil was obtained free of alcohol. This was shaken with water to remove sulphuric acid and dried *in vacuo* over phosphoric anhydride. The entire operation was carried out in an atmosphere of carbon dioxide to prevent oxidation to the disulphide.

Calculated for $HSCH_2CO_2C_2H_5$: S—26.7%; Found: S—23.4%.

This showed the presence of some alcohol in the oil but this could be disregarded for the purposes of this experiment.

Preparation of Ethyl Bismutho Thioglycollate.—36 Gm. of ethyl thioglycollate were treated with 26 Gm. of bismuth hydroxide following the method of Abel and Rowntree (2) in preparing the analogous antimony compound. The hydroxide was added in 2-Gm. portions as much heat was evolved. The oil was allowed to stand over night in the dark and was then freed from unreacted bismuth hydroxide and a trace of bismuth sulphide by filtration on a Buchner funnel. It was then dried *in vacuo* over phosphoric anhydride.

Calculated for $Bi(SCH_2CO_2C_2H_5)_3$: Bi—36.91%; S—16.99%.
Found: Bi—38.2 %; S—16.86%.

Preparation of Bismutho Thioglycollate Triamide.—An alcohol solution of ethyl bismutho thioglycollate was treated with ammonia gas dried by passing it over soda lime. Eventually an oil separated from the alcohol solution. The mixture was cooled and the ammonia bubbling was continued for one hour more. Then the flask was sealed and allowed to stand at room temperature for 48 hours. The

oil turned into a yellow solid which was freed of the mother liquor by decantation. This solid was contaminated by bismuth sulfide so that it was recrystallized from hot water. The yellow crystals obtained were very slightly soluble in cold water, soluble in hot water and glycerin.

Calculated for $Bi(SCH_2CO_2NH_2)_3$: Bi—43.6%; S—20.1%; N—8.7%.
Found: Bi—45.6%; S—20.58%; N—8.0%.

The biological tests on these compounds were carried out in the Biological Laboratories of E. R. Squibb and Sons, New Brunswick, N. J.

(1) Harden and Dunning, *J. Am. Chem. Soc.*, 49 (1927), 1017.
(2) Abel and Rowntree, *J. Pharmacol. & Exper. Therap.*, 2 (1910), 11.

RESEARCH DEPT. OF THE CHEMICAL & PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB & SONS, BROOKLYN, N. Y.

PHYTOCHEMICAL NOTES.*

No. 108. THE NON-HEPTANE CONSTITUENTS OF JEFFREY PINE OIL.

BY C. W. SONDERN.

Early in 1927 an understanding was reached with Dr. Graham Edgar of the Ethyl Gasoline Corporation of Yonkers, N. Y., in accordance with which a large amount of Jeffrey pine oil was to be sent to the Wisconsin Pharmaceutical Experiment Station for rectification of its principal constituent, the heptane. The non-heptane constituents were to be used for further investigation of these substances, whereas the heptane fraction was to be forwarded to Yonkers for the study of the standardization of gasoline as fuel in internal combustion engines. The Jeffrey pine oil was produced in California during the summer of 1927 as a coöperative enterprise between the Ethyl Gasoline Corporation, the local representative of the Bureau of Forestry, and a third party, the Chemical Corporation of California. The material, four drums in all, was received at Madison, in the fall of the same year.

The materials obtained in the separation of the heptane fraction from the Jeffrey pine oil may, for the sake of convenience, be grouped in the following manner:

I. The aqueous cohobate.
II. Oily fractions distilling below the b. p. of *n*-heptane ("Vorlauf").
III. The heptane fractions forwarded to the Ethyl Gasoline Corporation.
IV. Oily fractions distilling above the b. p. of *n*-heptane after removal of the aldehydes by shaking them with hot conc. $NaHSO_3$ solution.
V. The oily aldehydes regenerated from the sodium acid sulphite addition products.[1]
VI. Some resinous materials from drums and still which were discarded.

I. Examination of the Aqueous Cohobate.—The aqueous distillates collected in connection with the various fractionations in the first distillation of the Jeffrey pine oil were combined and concentrated. The original volume of nine gallons was distilled and the first third retained. This fraction was neutralized with barium carbonate and evaporated to three liters in a large still. The filtrate was further concentrated in an evaporating dish to one hundred cc. when the concentrate was

* From the Laboratory of Edward Kremers.
[1] P. A. Foote, JOUR. A. PH. A., 18 (1929), 350.