STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. III. IODOBISMUTHATES OF ALKALOIDS.*

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The alkaloids in combination with bismuth iodide have been known for a considerable time since Draggendorf (1) in 1866 utilized the bismuth iodide and hydriodic acid double salts to precipitate the alkaloids from acid solution. Since that time a number of investigators have studied the chemical composition and analysis of these substances including Pozzi-Escot (2), Aubry and Demelin (3), Azoulay (4), Francois and Blanc (5), (6), Bardet (7), Francois and Seguin (8), Isnard (9, 10), Rabak (11), and Ewe (12). More recently the iodobismuthates of quinine and emetine have received extensive use in the treatment of syphilis. The excretion, absorption and toxicity of these compounds have been studied by Lomholt (13), Jeanselme (14), and Lacapere, Restoux and Bugeard (15).

In this investigation the iodobismuthates of quinine and emetine were prepared by the methods already available and also the iodobismuthate of procaine was prepared.

These compounds are all insoluble in water and it was necessary, therefore, to inject them in oil suspension. As in the case of the fatty acid salts of bismuth and the bismuth tartrates, etc., the suspensions were injected intramuscularly into albino rats. The absorption was determined by estimating quantitatively the unabsorbed bismuth at the site of injection while the toxicity was estimated from the growth curves of the animals. The results obtained in these studies are given in the following table.

TABLE I.

Compound Injected.	Nature of Medium for Injection.	Bismuth Conc. Mg. Bi/Cc.	Approx. Maximum Tolerated Mg./Kg. Body Wt.	% Absorption.
Iosobismuthate of Quinine	Olive oil	20	Less than 400	50–60%
Iodobismuthate of Emetine	Olive oil	15	Less than 15	Slow
Iodobismuthate of Procaine	Olive oil	30	150	100%

These substances differ considerably in toxicity. The least toxic, the iodobismuthate of quinine, is, however, only 50 to 60% absorbed. This is not satisfactory from the therapeutic standpoint when such a result is compared to the rapidly and completely absorbed water-soluble compounds. The results obtained with the iodobismuthate of emetine were entirely unsatisfactory. In addition to being very slowly absorbed it was extremely toxic. Its high toxicity of less than 15 mg. per Kg. of body weight makes it unsuitable for therapeutic purposes. The iodobismuthate of procaine, a new compound, appears to be the best of this type of substance, although procaine cannot be classed as an alkaloid. The complete absorption of this compound coupled with the fact that it is not very toxic may be taken as an indication that it might be a satisfactory therapeutic agent. As a class, however, the iodobismuthates of the alkaloids in the form tested are not entirely satisfactory therapeutic agents because of their slow and incomplete absorption.

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EXPERIMENTAL PART.

Preparation of the Iodobismuthate of Quinine.—One gram of quinine hydrochloride was dissolved in 100 cc. of water. This was mixed with a solution of 1 Gm. of bismuth subnitrate in 4.7 Gm. of potassium iodide and 5 cc. of acetic acid in 100 cc. of water. The red precipitate which immediately formed was collected on a Buchner funnel and washed with water. This was then dried *in vacuo* over phosphoric anhydride.

Calculated for $C_{20}H_{24}N_2O_2$, 2HI, $2BiI_3$: Bi—23.7%; $C_{20}H_{24}N_2O_2$—18.7%. Found: Bi—23.7%; $C_{20}H_{24}N_2O_2$—19.2%.

Preparation of the Iodobismuthate of Emetine.—The same method as that used in the preparation of the quinine derivative was used here. The compound is a red powder.

Calculated for $C_{29}H_{40}O_4N_2$, HI, BiI_3: Bi—17.4%; $C_{29}H_{24}O_4N_2$—40.2%. Found: Bi—14.1%; $C_{29}H_{40}O_4N_2$—31.5%.

Preparation of the Iodobismuthate of Procaine.—One gram of bismuth subnitrate was dissolved in 5 cc. of hydrochloric acid and mixed with 4.7 Gm. of potassium iodide in 100 cc. of water. This was mixed with 1 Gm. of procaine hydrochloride dissolved in 100 cc. of water. The deep red precipitate which formed immediately was collected on a Buchner funnel, washed with water, and dried *in vacuo* over phosphoric anhydride.

Calculated for $C_{13}H_{20}N_2O_2$, 2HI, $2BiI_3$: Bi—12.3%; $C_{13}H_{20}N_2O_2$—22.89%. Found: Bi—14.5%; $C_{13}H_{20}N_2O_2$—21.70%.

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

(1) Draggendorf, *Pharm. Zeit. Russia*, 5 (1886), 82.
(2) Pozzi-Escot, *Ann. chim. anal.*, 12 (1907), 357.
(3) Aubry and Demelin, *J. pharm. chim.* (7), 25 (1922), 15.
(4) Azoulay, *Bull. Soc. Fr. Derm. & Syph.*, 29 (1922), 57.
(5) Francois and Blanc, *Compt. rend.*, 175 (1922), 169, 273.
(6) Francois and Blanc, *Bull. soc. chim.* (4), 33 (1923), 333.
(7) Bardet, Paris Thesis (1923).
(8) Francois and Seguin, *J. pharm. chim.*, 2 (1925), 59.
(9) Isnard, *Bull. sci. pharmacol.*, 30 (1923), 129.
(10) Isnard, *Ibid.*, 32 (1925), 78.
(11) Rabak, Report Lab. A. M. A., 11 (1918), 66.
(12) Ewe, JOUR. A. PH. A., 10 (1921), 261.
(13) Lomholt, *Hospitalstidende*, 67 (1924), 72.
(14) Jeanselme, *Bull. Soc. Fr. Derm. & Syph.*, 31 (1924), 348.
(15) Lacapere, Restoux and Bugeard, *Ibid.*, 31 (1924), 331.

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It may be that some day it will be said, "1932 was a hard year, but without it we would not have had the new tonic and cleansing resolves which will help us get out of the trough of the sea in which our ship was in danger of foundering."