completely removed from the paste by shaking out with hot water and passing the washings through a filter. The zinc oxide and other insoluble matter composing the base of the paste are retained by the filter. After ignition, the zinc oxide content can readily be determined by titration.

The above methods were also applied to the quantitative determination of resorcinol and zinc oxide in Mild Resorcinol Paste and they were found to be equally as well suited to the assay of this preparation as to the assay of the strong paste.

Since the methods described above are comparatively simple, give accurate and concordant results, it is recommended that they be adopted for admission to the National Formulary, and that the following standards be prescribed for the resorcinol pastes contained therein:

Suggested Standards: Strong Resorcinol Paste.—One hundred grams of Strong Resorcinol Paste contain not less than 19 Gm. and not more than 21 Gm. of $C_6H_4(OH)_2$, and not less than 19 Gm. and not more than 21 Gm. of ZnO.

Mild Resorcinol Paste.—One hundred grams of Mild Resorcinol Paste contain not less than 9.5 Gm. and not more than 10.5 Gm. of $C_6H_4(OH)_2$, and not less than 24 Gm. and not more than 26 Gm. of ZnO.

STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. II. BISMUTH SALTS OF ALIPHATIC HYDROXY ACIDS.*

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

A great deal of work has been done with one acid of this series, namely, tartaric acid. The sodium and potassium salts of this acid in combination with bismuth have been used extensively in the treatment of syphilis both in aqueous solution and in oil suspension. Also a number of investigators have studied both the preparation of these compounds and their absorption, excretion and toxicity in animals.

The composition of bismuth tartrates and their preparation by different methods have been described by Rosenheim and Vogelsang (1), Cowley (2), Bauer (3), Maschman (4), Warren (5), Corfield and Adams (6, 7), Barthe (8), Fabregue (9), Picon (10), Godfrin (11), Von Oettingen and Ishikawa (12), Volmer (13), Hehner and Likiernik (14), Kober (15), Von Oettingen, Sollmann and Schweid (16), and Yoe and Mote (17). The toxicity, absorption and excretion of these compounds have been discussed by Ducrey (18), Pautrier (19), Didry (20), Pomaret and Didry (21), Raiziss and Brown (22), Raiziss and Severac (23), Giemsa (24), Giemsa and Weise (25), Lomholt (26), and Pacella (27). Also Browning, Cohen, Gulbransen, Phillis and Snodgrass (28) studied the comparative therapeutic action of the bismuth salts of several organic hydroxy acids including tartaric acid, gluconic acid, mannonic acid and others. An investigation of the effect of different solvent media on the absorption of and local reactions produced by bismuth tartrates in dogs was reported by Jurist and Christiansen (29).

The purpose of this investigation was to compare the toxicity and absorption of bismuth tartrates in aqueous solution and in oil suspension with bismuth tartrates and bismuth mucates combined with mannite, and with bismuth mucates

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in aqueous solution. In these studies the same method was used in studying the absorption and toxicity as that used in the investigation of the bismuth salts of the fatty acids. The time allowed for absorption was extended to 60 days in this instance as compared to the 27- to 35-day period used in studying the fatty acids.

The preparations were injected intramuscularly into albino rats either in water solution or oil suspension. The per cent absorption was determined by killing the animal and estimating by analysis any bismuth remaining unabsorbed at the site of injection. The toxicity was determined as in the study of the fatty acid compounds from the growth curves of the albino rats. The following table contains the results obtained.

TABLE I.

Compound Injected.	Nature of Medium for Injection.	Dosage Mg. Bi/Cc.	Per Cent Absorbed.	Approximate Maximum Tolerated Dose Mg./Kg. Body Weight.
Sodium Tri-Bismuth Tartrate	Water	35	100	600
Sodium Tri-Bismuth Tartrate	Water	35	100	600
Sodium Tri-Bismuth Tartrate	10% Aqueous glucose	50	96	500
Sodium Tri-Bismuth Tartrate	10% Aqueous glucose	50	87	500
Sodium Tri-Bismuth Tartrate	Olive oil	35	...	600
Sodium Tri-Bismuth Tartrate	Olive oil	35	...	600
Sodium Potassium Bismuth Tartrate	10% Aqueous glucose	35	100	50
Potassium Tri-Bismuth Tartrate	Olive oil	33.5	37–81.5	400
Sodium Bismuth Tartro-Mannitan	Water	50	100	250
Sodium Bismuth Tartro-Mannitan	Olive oil	50	90	...
Sodium Bismuth Mucate	10% Aqueous glucose	50	90	300
Sodium Bismuth Muco-Mannitan	10% Aqueous glucose	50	90	400

These results demonstrate clearly the fact that water-soluble bismuth preparations are much more readily absorbed than the water-insoluble compounds; absorption of insoluble compounds is discussed in Paper I of this series. Even when administered in olive oil suspension there is a very high percentage of absorption, since this exceeds 90% in all but two instances in the series of twelve tests made. The only experiments giving wide variations in absorption were those with potassium tartrate in olive oil. The average absorption excluding the latter material which gave irregular results was 95%. With water solutions and 10% aqueous glucose solutions the absorption was nearly complete in 72 hours. A more extended period was required for the absorption of the olive oil suspensions.

The toxicity of the tartrates was a little less than that of the mucates and it was also less than that of the complex compounds with mannite. The single exception was sodium potassium bismuth tartrate. This substance was far more toxic than the other tartrates although there was little difference in the completeness and rapidity with which they were absorbed. However, with this single exception, all of the bismuth derivatives of tartaric and mucic acids tested were relatively low in toxicity.

The completeness and rapidity with which these water-soluble compounds are absorbed and their low toxicity indicate that they are more satisfactory therapeutic

agents than the bismuth salts of the fatty acids. However, the objection to these compounds is their tendency to produce local reactions of some severity at the site of injection as was pointed out in a previous publication (29).

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

EXPERIMENTAL PART.

Preparation of Sodium Bismuth Mucate.—Five and six-tenths grams of mucic acid were dissolved in 600 cc. of water and 155 cc. of a bismuth subnitrate solution, prepared by dissolving 150 Gm. of bismuth subnitrate in 150 cc. of concentrated nitric acid (sp. gr. 1.41) made up to one liter with water, are mixed and a white precipitate is formed. This was collected on a Buchner funnel and washed with water, alcohol and ether; 10 Gm. of this solid were suspended in 100 cc. of water and dissolved by means of sodium hydroxide. An equal volume of 95% alcohol was added and a white precipitate formed. This was collected on a Buchner funnel, washed with alcohol and ether and dried.

Calculated for $CO_2Na—CHOBiO—CHOBiO—(CHOH)_2—CO_2Na$: Na—6.55%, Bi—59.6%. Found: Na—6.1%, Bi—60.1%.

Preparation of Sodium Bismuth Muco-Mannitan.—Thirty-seven and one-tenth grams of sodium bismuth mucate and 30 Gm. of mannite were dissolved in about 200 cc. of water and neutralized with 20% sodium hydroxide. After warming for $^1/_2$ hour on the steam-bath the solution was cooled and twice the volume of acetone was added. A brown syrup precipitated. The supernatant liquor was decanted and the residue was washed several times with acetone, and then with absolute alcohol and ether. A finely divided white powder was obtained.

Calculated for $CO_2Na—HCOBiO—(C_6H_{10}O_4)_2—(CHONa)_2—CHOBiO—CO_2Na—(C_6H_{10}O_4)$: Bi—31.5%; Na—6.9%; acetyl number, 20.0. Found: Bi—30.09%; Na—5.87%; acetyl number, 19.6.

Preparation of Sodium Tribismuth Tartrate.—Eighty-six cc. of a solution, prepared by dissolving 150 Gm. of bismuth subnitrate in 150 cc. of concentrated nitric acid and then diluted to one liter with water were run into 200 cc. of sodium hydroxide solution containing 8 Gm. of sodium hydroxide. The suspension was adjusted with concentrated nitric acid until weakly alkaline to litmus. The bismuth hydroxide so obtained was then collected on a Buchner funnel and washed with water. The freshly prepared, wet bismuth hydroxide was then suspended in 50 cc. of water, and 40 cc. of a solution containing 8 Gm. of tartaric acid and 4.3 Gm. of sodium hydroxide were added. The mixture was heated on the steam-bath for two hours and then cooled. The small amount of insoluble matter was removed by filtration. The clear filtrate was then treated with an equal volume of 50% alcohol. A white precipitate gradually separated. The solid was collected on a Buchner funnel, washed with 95% alcohol and ether. The dry white powder was readily water soluble.

Calculated for $C_4H_2O_9Bi_3Na$: Bi—74.29%. Found: Bi—72.33%.

Preparation of Potassium Tribismuth Tartrate.—The method used was the same as that used for the sodium salt except that potassium hydroxide was used instead of sodium hydroxide.

Preparation of Sodium Bismuth Tartro-Mannitan.—Eighty-six cc. of the same bismuth nitrate solution used above were treated with 40 cc. of an aqueous solution of 8 Gm. of tartaric acid while stirring at room temperature. After standing for 10 minutes 21.8 Gm. of sodium bicarbonate in 250 cc. of water were added. Vigorous effervescence occurred with the formation of a white precipitate. The mixture was heated for 30 minutes at 85° C., then the mixture was allowed to stand over night. The white solid was collected on a Buchner funnel and washed with water. The product was insoluble in water but soluble in aqueous sodium hydroxide, 10 Gm. of this solid, 10 Gm. of mannite and 150 cc. of water were treated, warm with dilute aqueous sodium hydroxide until a clear solution resulted. This solution was treated with two volumes of acetone precipitating a yellow oil. After the supernatant liquor was poured off, the oil was further washed successively with acetone and ether and converted into a solid by treatment with absolute alcohol. The solid so obtained was washed with absolute alcohol and ether. The solid was water soluble and contained 30.99% of bismuth, 6.68% of sodium and 35.92% of mannite calculated from the acetyl number.

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