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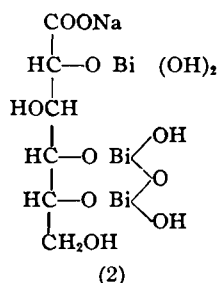
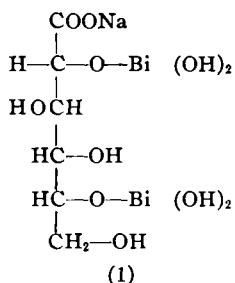
A STUDY OF BISMUTH SALTS OF GLUCONIC ACID.*

BY W. M. LAUTER AND H. A. BRAUN.¹

Most of the bismuth preparations which have been introduced into medicine for the treatment of syphilis fall into one of the three following groups: (1) water-soluble compounds, (2) oil-soluble compounds, (3) suspensions of insoluble compounds. These groups are named in the order of decreasing rates of absorption and excretion. The choice of a bismuth preparation depends largely upon the rapidity with which it is desired to obtain an effective bismuth concentration in the tissues and also upon the frequency of injection.

Von Oettingen, Ishikawa and Sollmann (1) have described the preparation and constitution of water-soluble mono- and di-bismuthyl citrates. Kober (2) has prepared water-soluble bismuthyl tartrates of very high bismuth content by shaking bismuth hydroxide with sodium tartrate.

Since the water-soluble bismuth salts of gluconic acid have not been described in the literature, a study of these compounds was undertaken using a method of preparation similar to that described by Kober (2). A mono-sodium-di-bismuthyl gluconate (Formula 1) and a mono-sodium-tri-bismuthyl gluconate (Formula 2) have been prepared. Also a product of still higher bismuth content was obtained which apparently is a mixture.



EXPERIMENTAL.

Preparation of Sodium-Di-Bismuthyl Gluconate.—Three hundred and forty-four cubic centimeters of a bismuth subnitrate solution, prepared by dissolving 306 Gm. BiONO_3 in 300 cc. of concentrated HNO_3 and made up to a volume of two liters with water, are poured slowly, while cooling, into a sodium hydroxide solution containing 32 Gm. NaOH in 800 cc. H_2O . The bismuth hydroxide is filtered at once and carefully washed with water.

The still moist bismuth hydroxide is then suspended in 150 cc. of water and a solution of 12.3 Gm. of gluconic acid in 12.3 cc. of water and 2.5 Gm. NaOH is added to the suspension. The liquid becomes clear and is filtered. The volume is 225 cc. The bismuth salt is now precipitated with 225 cc. of alcohol. A sticky white mass is obtained. The supernatant liquid is decanted, the

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precipitate redissolved in 100 cc. of water and reprecipitated with the same volume of alcohol. The precipitate is again separated from the supernatant liquid and again redissolved in 150 cc. water. One hundred and fifty cubic centimeters of alcohol are added slowly and the bismuth salt is now obtained as crystals free from sodium gluconate. It is filtered, washed with 150 cc. 50 per cent alcohol, followed by 95 per cent alcohol and finally with ether. The white crystals are dried at room temperature in a vacuum desiccator. The yield was 48.5 Gm. or nearly quantitative. This material when dried to constant weight at 100° lost 9.6 per cent water of crystallization. The product dried at 100° was analyzed for bismuth by the sulphide method.

Analysis: $C_6H_{13}O_{11}NaBi_2$ (Formula 1).

Calculated: 59.55% Bi. Found: 59.63% Bi.

In aqueous solution containing 12 mg. of bismuth per cc., the p_H is 9.4. When buffered to a p_H of 8.7 the solution resists heating at 100°.

Preparation of Sodium-Tri-Bismuthyl-Gluconate.—A solution of 306 Gm. $BiONO_3$ in 300 cc. concentrated nitric acid made up to a volume of 2 liters with water is prepared.

Six hundred and eighty-eight cubic centimeters of this solution are poured carefully into a cooled solution of 64 Gm. NaOH in 1600 cc. water. The precipitated bismuth hydroxide is filtered and thoroughly washed with water. The precipitate is then resuspended in water, filtered again and washed again. It should never be allowed to become dry. The hydroxide is then suspended in 200 cc. water and shaken for 30 minutes with a solution of 20 Gm. gluconic acid in 20 cc. water and 17.2 Gm. sodium hydroxide. A slight raise of temperature can be observed. The solution is filtered. The volume is approximately 300 cc. The solution is now poured slowly, while stirring, into an equal volume of alcohol. The white precipitate is filtered. It is washed once with 300 cc. 50 per cent alcohol, followed by 95 per cent alcohol. The precipitate is then redissolved in 200 cc. water and reprecipitated with 200 cc. alcohol. This precipitate is filtered and washed with alcohol. After drying at room temperature for 16 hours in a vacuum desiccator, the yield is 64 Gm. This material when dried to constant weight at 100° lost 21.3 per cent water of crystallization. The product dried at 100° was analyzed for bismuth by the sulphide method.

Analysis: $C_6H_{12}O_{12}NaBi_3$ (Formula 2).

Calculated: 67.71% Bi. Found: 67.61% Bi.

As a check on the purity of this product a 15-Gm. portion was redissolved in 100 cc. of water and 1 drop of *N* NaOH added. The product was precipitated by adding 100 cc. of alcohol and collected by centrifuging. It was washed with 150 cc. of 50 per cent alcohol followed by 150 cc. of 95 per cent alcohol and dried in a vacuum desiccator; 8.5 Gm. were recovered. This material when dried to constant weight at 100° lost 22.6 per cent water of crystallization. The product dried at 100° was analyzed for bismuth by the sulphide method.

Analysis: $C_6H_{12}O_{12}NaBi_3$ (Formula 2).

Calculated: 67.71% Bi. Found: 67.59% Bi.

These results show that the composition of the compound is not changed by reprecipitation.

A Gluconate of Higher Bismuth Content.—Kober (2) has prepared sodium-tetra-bismuthyl tartrate by shaking sodium tartrate with bismuth hydroxide for six days. Using a similar procedure we have attempted to prepare sodium-tetra-bismuthyl gluconate.

One hundred and fifty-three grams bismuth subnitrate were dissolved in 203 cc. concentrated nitric acid and made up to a volume of 1125 cc. with water. The bismuthyl hydroxide was precipitated with 225 cc. 50 per cent NaOH solution. The hydroxide was filtered and washed. Seventeen grams gluconic acid, dissolved in 17 cc. water and 14 cc. 50 per cent NaOH solution, were shaken at room temperature for 8½ days. The suspension was filtered and washed. An equal volume of alcohol was added to the solution and the product isolated by centrifugation and washed by centrifuging with 50 per cent alcohol, followed by 95 per cent alcohol and finally with ether. A yield of 96 Gm. was obtained.

The vacuum-desiccator-dried product lost 34.8 per cent moisture when dried to constant weight at 100°. Analysis by the sulphide method indicated 73.58 per

cent Bi. However, when this product was redissolved in water, reprecipitated with alcohol and dried to constant weight in a vacuum desiccator, it was found to contain only 6.97 per cent moisture removable by drying at 100°. The product dried at 100° analyzed 71.1 per cent Bi and was found to be insoluble in water. Thus our attempts to obtain a water-soluble tetra-bismuthyl gluconate corresponding to Kober's tetra-bismuthyl tartrate were unsuccessful.

Toxicity of the Bismuthyl Gluconates.—These preparations were dissolved in water so that each cc. contained 12 mg. of metallic bismuth and injected intravenously in rats. This route of administration is not used clinically but has been employed by a number of laboratory workers for rapidly estimating the systemic toxicity of various water-soluble bismuth compounds.

Preliminary experiments seemed to indicate that the tri-bismuthyl gluconate was somewhat less toxic than the di-bismuthyl gluconate. However, more complete studies using a large number of rats indicated that all these gluconates are approximately equally toxic. The minimum fatal dose was found to be approximately 7 mg. of bismuth metal per kilo and death occurred on the second to fifth day after injection. Parallel injections of water-soluble citrates and tartrates gave results indicating a similar toxicity.

These results indicate that these various water-soluble bismuth preparations when injected intravenously in rats in equivalent doses of metallic bismuth are approximately equally toxic. The wide differences in the intramuscular toxicities of numerous water-soluble bismuth preparations reported from the literature by Hanzlik, Seidenfeld and Johnson (3) are probably due in large part to differences in rates of absorption from the muscle. When such preparations are injected intravenously the factor of absorption is not introduced and the toxicities are greater and show lesser individual variation.

SUMMARY.

A mono-sodium-di-bismuthyl gluconate and a mono-sodium-tri-bismuthyl gluconate have been prepared containing 59.6 per cent and 67.6 per cent bismuth, respectively. When injected intravenously in aqueous solution into rats these compounds show a minimum fatal dose of approximately 7 mg. of metallic bismuth per Kg. which agrees with a similar toxicity observed for some water-soluble tartrates and citrates which were injected in parallel groups of rats.

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MERCURY DERIVATIVES OF AZO DYES.*¹

BY W. BRAKER AND W. G. CHRISTIANSEN.

Azo dyes such as the hydrochloride of 2,4-diamino-4'-ethoxy azobenzene (compound I)

* Scientific Section, A. Ph. A., Portland meeting, 1935.

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