Patented Mar. 20, 1928. **1,663,201**

UNITED STATES PATENT OFFICE.

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PROCESS FOR MAKING BISMUTH TARTRATES AND PRODUCT PRODUCED THEREBY.

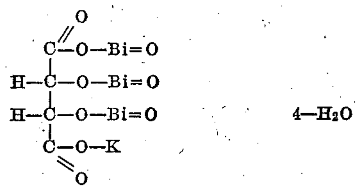
No Drawing. Application filed May 28, 1926. Serial No. 112,398.

This invention relates to improvements in the manufacture and composition of bismuth tartrates, especially intended for the treatment of syphilis.

The use of bismuth therapy in syphilis since its introduction in France a few years ago has gradually grown so that it has become a valuable addition to our regular antisyphilitic chemotherapeutic agents, the arsenicals.

L. E. Warren of the Chemical Laboratories of the American Medical Association, (Journ. Amer. Med. Ass. 84, 1067, 1925) writing under the title "What is the composition of bismuth tartrates used in the treatment of syphilis", stated as part of his summary that "the fact that the bismuth content in the various bismuth preparations—the satisfactory as well as the unsatisfactory—is within such a wide range (31–73%) emphasizes the necessity for clinicians to inquire carefully concerning the composition of the bismuth products they use, particularly in reference to the bismuth content, before making reports concerning the alleged effectiveness of this, that or the other preparation". This statement was based upon analyses of practically all, seven in number, of the bismuth preparations on the market.

Theoretically and actually found, there are many different compounds of bismuth and tartaric acid. Of the water soluble preparations which are probably more effective on account of speedier absorption and greater penetration, all of them also contain in addition to bismuth and tartaric acid, alkali metals, either sodium or potassium or both. Ordinary bismuth salts of tartaric acid have too great a tendency to hydrolyze into insoluble bismuth oxide or basic salts to be desirable for syphilitic treatment. Therefore the more firmly the bismuth is bound to the tartaric acid, in the form of a complex salt, the greater efficacy can be expected as the bismuth must remain in the form of a soluble organic complex long enough to allow absorption from the site of injection and to be distributed throughout the body by means of the blood stream. Chemical tests show that the most firmly bound bismuth compounds of those heretofore isolated, are the tri-bismuth alkali tartrates, of which the only known example is potassium tri-bismuth tartrate. The following formula has been assigned to this compound:



Anhydrous 72.8% Bismuth

With water of hydration 67.1% Bismuth

This compound and its preparation was first described by Rosenheim and Vogelsang (Zeitschrift für Anorg. Chem. 48, 205, (1906)) and has been on the market and used clinically both here and abroad.

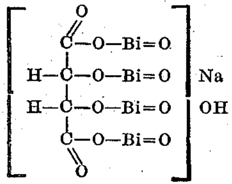
So far as I am aware no similar sodium product has been prepared, although theoretically it might have some advantages over the potassium compound. To many workers in pharmacology and medicine, potassium compounds of therapeutic agents are not so desirable as the corresponding sodium compounds. On this subject the U. S. Dispensatory (twentieth edition) states on page 912 that "while the presence of a certain amount of potassium in the blood is essential for vital activity, a very slight increase in its percentage has a deleterious influence on many organs. The injection of a potassium salt into the circulation weakens the contractile power of all muscle fibers but affects especially the heart and blood vessels. It also exercises a marked depressant action upon the central nervous system, including the spinal cord, brain and medulla. Although the depressant action of potassium is strong when injected directly into the blood stream, when taken by the mouth it exercises very little influence upon the circulation. This is due to the fact that it is excreted by the kidneys so rapidly that it cannot be absorbed in sufficient amounts through the alimentary tract to cause accumulation of a poisonous dose in the blood". I believe also that the depressant action of injected potassium may be due to the fact that the potassium salts cannot become diluted with the body fluids, at once, and that for a time certain parts of the body and the circulating system are exposed to too great a concentration of the potassium salt.

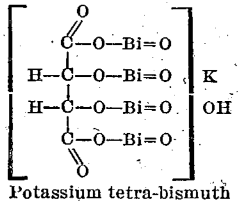
For these reasons a sodium tri-bismuth tartrate seemed desirable and of value. No method was available in the literature which described the isolation of such a sodium compound. Rosenheim and Vogelsang attempted to isolate the sodium compound but they stated it would not crystallize out similarly to the potassium compound. Klauder makes the statement that the sodium salt is unstable which indicates in the light of the work reported here that the sodium compound had not been successfully isolated, or at least a sodium compound similar to the one described in this disclosure had not been isolated.

On considering the method of Rosenheim and Vogelsang, which consists in digesting bismuth subnitrate with tartaric acid and an excess of alkali while heating, I came to the conclusion, that from thermo-dynamic reasoning, the reaction ought to be conducted in the cold or at least without heating. Furthermore since the nitrate group does not enter into the composition of the compound desired, its presence may interfere with the reaction. For these reasons I tried the reaction with a slight excess of sodium hydroxide in the cold, using bismuth hydroxide as a source of bismuth and shaking with a mechanical shaker. The bismuth hydroxide at first dissolved fairly rapidly, but soon it dissolved more and more slowly. However a number of experiments showed that the longer I shook the mixture, the more bismuth hydroxide dissolved. At the end of about 144 hours (6 days about) the mixture seemed to come to an equilibrium and no more bismuth hydroxide seemed to dissolve. On filtering I had in solution, of course, a sodium bismuth tartrate. A few experiments with small portions of the filtrate soon showed that a half volume of 95% alcohol gave me a copious yield of precipitate. The precipitate after washing with 50% alcohol several times to remove the mother liquor and finally with 95% alcohol and drying in the air at room temperature gave a water soluble powder containing 72.9% of bismuth and 4.6% of water of hydration, or for an anhydrous substance 76.4% of bismuth. Since the anhydrous sodium tri-bismuth tartrate could not contain more than 74.2% of bismuth, it was evident that this preparation contained more than three molecules of bismuth. The theoretical per cent for bismuth and water for sodium tetra-bismuth tartrate and sodium tri-bismuth tartrate is as follows:

	Anhydrous	$1H_2O$		$3H_2O$	
		H_2O	Bi	H_2O	Bi
Theory for tri-bismuth tartrate	74.2% Bi	2.09%	72.7%	6.01%	69.6%
Actually found	76.4% Bi	------	--------	4.60%	72.9%
Theory for tetra-bismuth tartrate	77.1% Bi	------	--------	4.73%	73.2%

From this data I was forced to the conclusion that this sodium tartrate compound was sodium tetra-bismuth tartrate and I have tentatively assigned the following formula to it.


Sodium tetra-bismuth tartrate 77.1% Bi


Potassium tetra-bismuth tartrate 75.8%

If these findings and conclusions with the sodium compound were correct, then it ought to be possible to get a potassium compound of similar composition with even more bismuth content than any found on the market, since most of them approximate in bismuth content that of a tri-bismuth tartrate.

On substituting potassium hydroxide for sodium hydroxide in the method developed for the sodium compound, I had no difficulty in getting a fair yield on the first trial using otherwise the exact technic as I did for the sodium process. It is probable that by using more suitable proportions of alcohol, since the solubilities of the two substances undoubtedly differ, a greater yield would have been obtained. However, the analytical data agree with the theory for a tetra-bismuth tartrate even more closely than did the sodium compound:

Potassium compound	Anhydrous Bi%	$1H_2O$		$2H_2O$	
		H_2O%	Bi%	H_2O%	Bi%
Theory for tri-bismuth tartrate	72.9	2.05	71.4	4.02	70.0
Actually found	75.8	------	------	2.76	73.8
Theory for tetra-bismuth tartrate	75.8	------	------	3.16	73.3

These tetra-bismuth tartrates are finely divided powders, odorless and tasteless, permanent in the air at ordinary temperatures. At higher temperatures they seem to suffer a change, probably absorbing carbon dioxide and other acid vapors from the air, so that they require additional alkali before they will dissolve in water. On contact with water, these preparations first gel and then dissolve. Accurate solubility determinations have not yet been made, indications are that the solubility at room temperatures is nearly forty per cent, one part of water does not dissolve quite one part of these tetra-bismuth tartrates, whereas one and a half parts usually do.

Solutions of these tetra-bismuth tartrates are alkaline in harmony with the formula, and so far as we know are perfectly stable. The alkalinity can be decreased by titrating with N/10 sulphuric acid, using phenolphthalein as an indicator, to a hydrogen ion concentration of a P_H 8.4–8.6, at which point the solutions up to 10% seem stable indefinitely. Heating such solutions to 70 C. for 45 minutes seems to cause no change whatever, while heating 5 minutes at 100 C. produced only a very slight cloud and a slight increase in alkalinity, but which on cooling slowly returned to its original state.

The alkalinity can be also decreased by absorption of iodine, with the formation of colorless solutions of iodides and iodates of the tetra-bismuth tartrates, which also seem stable at room temperatures.

On adding a gram equivalent of acid to solutions of tetra-bismuth tartrates a precipitate is produced, which redissolves in an equivalent amount of alkali, indicating that the precipitate is a tetra-bismuth tartrate base. Large excess of acids decompose the base so that it does not redissolve in an equivalent amount of alkali. This base is very gelatinous and seems to be close to a permanent suspensoid.

Raiziss, Severac and Winicov (Amer. Journ. of Clin. Med. August 1923) quote Sazerac and Levaditi, who were the first to study bismuth tartrates as curative agents for syphilis, as stating that their sodium and potassium bismuth tartrate killed white rats when 5 milligrams per kilogram of animal was injected intravenously. Raiziss and associates found their potassium tribismuth tartrate was tolerated up to 10 milligrams per kilogram, but killing at 15 milligrams per kilogram. Our preliminary results with white rats indicate that these tetra-bismuth tartrates are considerably less toxic being tolerated when injected intravenously up to about 25 milligrams per kilogram of body weight.

The results of my investigation as above described confirm my belief that the temperature at which the reaction between the alkali and the bismuth compound is carried out is important in determining whether the tri-bismuth tartrates or the tetra-bismuth tartrates will be formed. One of the essential features of my process of producing the new compound, therefore, consists in so regulating the temperature at which the reaction is carried on that it shall be maintained below a point where substantial amounts of tri-bismuth tartrates are formed.

The following example for the preparation of these tetra-bismuth tartrates is given in detail, but those skilled in the art will know how to make various modifications in proportions and amounts of the materials used and by using different alkalies or combinations of them effect the production of tetra-bismuth tartrates, without departing from the general disclosures herein set forth:

Two hundred grams of bismuth subnitrate were dissolved in 270 cc. of concentrated nitric acid and made up with water to about 1500 cc. Then with rapid stirring 300 cc. of saturated sodium hydroxide (50%) were added to precipitate the bismuth as hydroxide in a finely divided condition. The precipitate was then filtered upon a suction filter, washed and resuspended in water, filtered, washed with distilled water three or more times until all of the mother liquor had been removed.

Into a liter bottle or flask were weighed 25.0 grams of tartaric acid and 75 cc. of distilled water added. Then 28 cc. of saturated sodium hydroxide (50%) were added with stirring and cooling. When the liquid had cooled to 14–15 C. the bismuth hydroxide, prepared as described above was added and after stoppering the bottle or flask securely, the mixture was shaken on a mechanical shaker for from one hour to two hours, at three hour intervals during the first day. This shaking was repeated two or more times a day for 6 to 7 days. Longer standing or shaking caused no harm, but the amount of bismuth hydroxide dissolved by the alkaline tartrate solution was but slightly increased over the amount dissolved during the first six days. Attempts to shorten the period by heating decreased the amount and purity of the yield.

The mixture at the end of six days was filtered through a porous glass Buchner suction filter or through a hard filter paper. After washing the undissolved bismuth hydroxide with 50 cc. of distilled water, the total filtrate equalled 350 cc.

On adding 175 cc. of 95% alcohol to the filtrate with stirring, a copious precipitate was obtained, which was filtered on a Buchner funnel with suction, washed and suspended in 100 cc. of 50% alcohol, filtered and washed, resuspended, filtered and washed with 95% alcohol three or four times or until the filtrate was neutral to litmus paper. After drying at room temperature for several days, the yield was in the neighborhood of 125 grams or 89%. On substituting the same proportion of potassium hydroxide for sodium hydroxide, the yield was about 30%.

That these tetra-bismuth tartrates have never before been isolated is indicated by the high content of bismuth, by the stability of the aqueous solutions, and by the relatively low toxicity, ½ to ⅓ of that of the products made by Raiziss and ⅕ of that made by Sazerac and Levaditi, the French originators of bismuth therapy.

Since in this disclosure I have shown how to form these new salts or compounds easily, and therefore have demonstrated the fundamental conditions under which such compounds are made, it will be understood that other alkalies, such as ammonium and lithium, etc., can be used to produce the corresponding compounds, or that any combination of alkalies may be used to replace a single alkali, producing a bismuth tartrate containing in its composition two or more different alkalies. Furthermore since the base containing four atoms of bismuth to every molecule of tartaric acid can be isolated, by simple neutralization and otherwise, and will dissolve in a gram equivalent of alkali, a solubility greatly in excess of that shown by the bismuth compounds heretofore considered suitable for such purpose, it is particularly well adapted for use in medicine generally as well as for the particular application above mentioned. Accordingly, the invention is to be given a broad interpretation and the composition and process are not to be limited in proportions or procedure other than as indicated in the appended claims.

What is claimed is:

1. A process for making bismuth tartrates which consists in treating a basic bismuth compound with an alkali and tartaric acid at not exceeding normal room temperature.

2. A process of making bismuth tartrates which consists in treating a basic bismuth compound with an alkali metal hydroxide and tartaric acid at a temperature promoting the formation of a tetra-bismuth tartrate, but sufficiently low to prevent the formation of substantial amounts of tri-bismuth tartrates.

3. A process for making bismuth tartrates which consists in treating a basic bismuth compound with an alkali and tartaric acid at not exceeding normal room temperature, separating off the excess of bismuth salts, and precipitating the bismuth tartrate with alcohol, substantially as described.

4. A process for making a sodium bismuth tartrate comprising treating a basic bismuth compound with sodium hydroxide and tartaric acid at not exceeding normal room temperature.

5. A process of making sodium bismuth tartrate which consists in treating bismuth hydroxide with sodium hydroxide and tartaric acid at not exceeding normal room temperature.

6. A process for making a sodium bismuth tartrate comprising treating a basic bismuth compound with sodium hydroxide and tartaric acid at not exceeding normal room temperature, separating off the excess bismuth salts, and precipitating the sodium bismuth tartrate with alcohol, substantially as described.

7. A process for making an alkali metal bismuth tartrate comprising treating a basic bismuth compound with an alkali metal hydroxide and tartaric acid at not exceeding normal room temperature.

8. A process of making an alkali metal bismuth tartrate comprising treating bismuth hydroxide with an alkali metal hydroxide and tartaric acid while maintaining the temperature at not exceeding normal room temperature.

9. A process for making an alkali metal bismuth tartrate comprising treating a basic bismuth compound with an alkali metal hydroxide and tartaric acid at not exceeding normal room temperature, separating off the excess bismuth salt, and precipitating the alkali metal bismuth tartrate with alcohol, substantially as described.

10. A process for making alkali metal tetra-bismuth tartrates comprising treating a basic bismuth compound with an alkali metal hydroxide and tartaric acid at not exceeding normal room temperature.

11. A process of making alkali metal tetra-bismuth tartrates which comprises treating bismuth hydroxides with a solution of an alkali metal hydroxide and tartaric acid at approximately 14–15° C.

12. A process for making an alkali metal tetra-bismuth tartrate comprising treating a basic bismuth compound with an alkali and tartaric acid at not exceeding normal room temperature, separating off the excess bismuth salts, and precipitating the alkali metal tetra-bismuth tartrate with alcohol, substantially as described.

13. A soluble bismuth tartrate having over 72.9% of bismuth.

14. A soluble alkali metal bismuth tartrate having over 72.9% of bismuth.

15. An alkali metal bismuth tartrate having four atoms of bismuth for every molecule of tartaric acid.

16. A bismuth tartrate having four atoms of bismuth for every molecule of tartaric acid.

17. A sodium bismuth tartrate having four atoms of bismuth to every molecule of tartaric acid.

In testimony whereof, I have signed my name to this specification this twenty-second day of May, 1926.

PHILIP ADOLPH KOBER.