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THERAPEUTIC PREPARATION OF BISMUTH AND METHOD OF PREPARING SAME

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5 Claims. (Cl. 260—344)

The present invention relates to therapeutic preparations for the administration of bismuth, antimony and arsenic into the human organism.

The present application is a continuation-in-part of my copending application Serial No. 745,527, filed September 26, 1934.

A number of organic compounds of bismuth, antimony and arsenic are now in use for the treatment of various diseases, such as syphilis and trypanosomiasis, but their application is frequently attended by irritation and even poisoning, and sometimes gives rise to dermatitis, gingivitis and other affections. While these detrimental side effects are generally due to the susceptibility of the patient to bismuth, antimony and arsenic poisoning, they are frequently due, at least in part, and sometimes perhaps even entirely, to the other constituents of the medicinal compound. It is my belief that the untoward effects, or a great part of them, obtained with the use of known compounds of the above-named metals can to a great extent be traced to the fact that the remainder of the molecule is just as foreign to the human organism, and particularly to the blood stream, as the metal it is sought to introduce, and just as poisonous or difficultly tolerable, so that the system receives a double shock from both the therapeutic metal and the organic radical to which it is joined.

It is accordingly the general object of the invention to provide new preparations of bismuth, antimony and arsenic, constituting group Vb of the periodic system, having spirochaetocidal and trypanosomicidal activity and characterized by being considerably less toxic than the known preparations containing these metals and currently used in the treatment of syphilis, trypanosomiasis and kindred diseases.

It is a further object of the invention to provide therapeutic preparations of bismuth, antimony and arsenic which can be more readily tolerated by the human organism and possess the unique property of inhibiting the tendency to dermatitis and gingivitis commonly observed during bismuth, antimony and arsenic therapy. Other objects and advantages of the invention will appear from the more detailed description hereinbelow.

In accordance with the present invention, the bismuth, antimony and arsenic are administered in the form of the cevitamate or laevo-ascorbate in dosages common for these metals. I have found that the cevitamic acid radical offers an unusually effective and non-toxic vehicle for the introduction of these otherwise poisonous metals or metalloids into the human organism. The peculiar structure of cevitamic acid, which supplies both oxidation and reduction mechanisms, makes it a remarkable detoxicating agent and the bismuth, antimony and arsenic cevitamates are thus less toxic and more easily tolerated by the body than known preparations of bismuth, antimony and arsenic. It is currently believed that antiluetic preparations are rendered more active when subjected to the oxidizing and reducing substances of the body. I have found that the cevitamate radical exerts this action when combined with bismuth, antimony and arsenic and thus increases the activity of the metal while at the same time reducing its toxic effects.

I have found further that the cevitamic acid compounds of the above named metals are quite soluble in water and with the aid of a stabilizing agent, and particularly at a pH value of about 7.6 or slightly higher, can be kept indefinitely in solution. Moreover, these salts possess also the physiological action of cevitamic acid, and thus simultaneously act to correct morbid conditions arising from a deficiency of vitamin C.

My invention will be further described with the aid of the following examples which are presented purely by way of illustration and not as indicating the scope of the invention:

EXAMPLE 1.—*Preparation of bismuth cevitamate*

1.8 cevitamic acid (about .01 mol) were dissolved in 20 cc. glycerol and 10 cc. N NaOH. To this were then added under stirring and cooling 35 cc. N NaOH and 22.5 cc. $Bi(NO_3)_3 5H_2O$ (containing $\frac{2}{300}$ mol) in the following order:

NaOH	$Bi(NO_3)_3 5H_2O$
(1) 5 cc	(2) 2.5 cc.
(3) 5 cc	(4) 2.5 cc.
(5) 5 cc	(6) 2.5 cc.
(7) 5 cc	(8) 2.5 cc.
(9) 5 cc	(10) 2.5 cc.
(11) 5 cc	(12) 2.5 cc.
(13) 5 cc	(14) 7.5 cc.

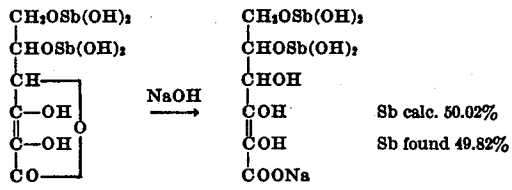
In this way the solution was always kept alkaline until the final addition of the $Bi(NO_3)_3$. The orange colored precipitate was centrifuged, and then washed four times with distilled water by centrifugation. The moist precipitate weighing approximately 5 g. when dry theory 5.5 g.) was suspended in 100 cc. 50% glycerol and 5N NaOH was dropped in under stirring until a faint cloudiness persisted. The solution was filtered through

a filter cell and to the filtrate 2.5 cc. Na_2SO_3 solution (containing 250 mg.) were now added to stabilize it and it was brought down to a pH around 7.6 with excess cevitamic acid. It was then made up to 150 cc. with distilled water and bottled immediately. The preparation should contain approximately 20 mg. Bi per cc.

EXAMPLE 2.—*Preparation of antimony cevitamate*

1.8 g. cevitamic acid were dissolved in 10 cc. saturated saline (NaCl) solution. To this was added slowly under stirring 4.3 g. $SbCl_3$ dissolved in 20 cc. saturated saline solution. The acid solution was cooled with ice, and under stirring and cooling 12 cc. 5N NaOH saturated with salt were added. This left the solution still acid. The precipitate was centrifuged, and was then washed three times by centrifugation with distilled water. The moist precipitate weighing 4.8 g. when dry (theory 4.9 g.) was now suspended in 100 cc. of 50% glycerol solution and 5N alkali solution was dropped in under violent stirring until a faint permanent cloudiness remained. The solution was filtered through a filter cell until clear. It should have a pH around 9.6. There were then added 2.5 cc. Na_2SO_3 (containing 250 mg.) to stabilize the solution. If a lower pH is desired a little excess cevitamic acid could be added. The solution was then made up to 150 cc. and bottled immediately. This solution should contain approximately 16 mg. Sb per cc.

The reaction may be represented as follows:



EXAMPLE 3.—*Preparation of arsenic cevitamate*

20 g. (100 cc.) arsenious chloride were dissolved in 50 cc. absolute alcohol and the solution shaken up with 1.8 g. cevitamic acid. Practically all the acid went into solution which would not have been the case if the arsenius chloride had been absent. This indicated the formation of arsenic cevitamate. The arsenic cevitamate is less toxic than currently used arsenic preparations in the treatment of syphilis. The pH may be adjusted with sodium hydroxide or other alkali.

The solutions of the cevitamates above described may be packaged in ampoules or if desired in the solid condition in the form of tablets. The compounds may be prepared in an indifferent atmosphere, like N_2 or CO_2, but this is not absolutely necessary; while if desired the ampoules may be charged in such an atmosphere or may have CO_2 dissolved in the solution.

Various organic acids can be employed for adjusting the pH to a lower alkalinity, care being taken to avoid precipitation. Tartaric, citric, gluconic and other injectible organic acids may be used for this purpose. To bring the pH down from above 9 to 8, tartaric or citric acid is satisfactory, whereas gluconic acid may cause precipitation.

Local anaesthetics such as chlorbutanol or benzyl alcohol may be added to reduce tissue sensitivity. They likewise have a desirable effect on the stability of the solution.

The bismuth, antimony and arsenic cevitamates are administered parenterally, preferably intramuscularly. The dosage may amount to 20 to 40 mg. of the metal once or twice weekly. They are all suitable for the treatment of syphilis and protozoan diseases, like trypanosomiasis.

In syphilis, various known arsenic and bismuth preparations will not influence the Wassermann reaction in some cases. These "Wassermann fast" cases responded better to bismuth cevitamate than to known bismuth and arsenic preparations.

In place of NaOH, other bases may be employed, such as KOH, Na_2CO_3, etc., while in place of cevitamic acid and a base, a salt of cevitamic may be used. The inorganic salts of bismuth, antimony and arsenic above named may be replaced by other salts having relatively non-toxic anions and capable of entering into double decomposition with cevitamates; if desired, the hydroxides of the metals may be used, but they generally react with cevitamic acid only with difficulty. The sodium sulphite may be used with or be substituted by the soluble salts of other weak acids, like these citrates, or by sucrose, organic acids like tartaric and citric acids, or other stabilizers which are suitable for injection. The cevitamates may be employed in the form of isotonic solutions, which may be prepared by the addition of a suitable quantity of sodium chloride or other salt thereto.

Variations from the specific methods of procedure above described will occur to those skilled in the art without departing from the spirit of the invention.

I claim:

1. The method of preparing a therapeutically valuable compound of bismuth, which comprises dissolving cevitamic acid in a suitable solvent, adding thereto a soluble bismuth salt, whereby a reaction takes place to form the metal compound of said acid, and isolating the reaction product.

2. The method of preparing a therapeutically valuable compound of bismuth, which comprises dissolving cevitamic acid in a suitable solvent, adding thereto a base and a soluble bismuth salt, whereby a reaction takes place to form the bismuth compound of said acid, and isolating the reaction product.

3. The method of preparing a new bismuth compound having therapeutic properties which comprises dissolving cevitamic acid in a suitable solvent, and adding thereto an alkali and a compound of bismuth capable of reacting with cevitamic acid, whereby a reaction takes place to form the bismuth compound of cevitamic acid.

4. The cevitamic acid compound of bismuth.

5. A therapeutic preparation comprising the solubilized reaction product of cevitamic acid and a compound of bismuth capable of reacting therewith.

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