Patented Jan. 10, 1933

1,893,872

UNITED STATES PATENT OFFICE

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METAL COMPLEX COMPOUND

No Drawing. Application filed June 4, 1931, Serial No. 542,190, and in Germany June 3, 1930.

The present invention relates to new water soluble neutral metal complex compounds suitable for therapeutic use and to a process of preparing same, said invention being a further development of our prior inventions described and claimed in U. S. Patents (copending applications Serial Nos. 446,405, filed April 22, 1930, and 500,434, filed December 5, 1930).

U. S. Patents (copending applications Serial Nos. 446,405, filed April 22, 1930, and 500,434, filed December 5, 1930) describe complex compounds of iron and antimony with aliphatic polyhydroxy carboxylic acids, said complex compounds may contain alkali metal or nitrogen bases as neutralizing agents.

In accordance with the present invention neutral complex compounds of metals other than iron, antimony, alkali and alkaline earth metals, but having an atomic number higher than 21, with aliphatic polyhydroxy carboxylic acids of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms, said complex compounds having been neutralized by alkali metal-or nitrogen bases, may be prepared. The process of manufacture of the new metal complex compounds is by reacting upon an aliphatic polyhydroxy carboxylic acid containing at least 5 carbon atoms and at least three hydroxy groups bound to three adjoining carbon atoms, with an oxide or hydroxide of a metal, other than antimony, iron, alkali and alkaline earth metals, but having an atomic number higher than 21, in aqueous solution and adding thereto such a quantity of an alkali metal-or nitrogen base that a neutral complex compound is formed.

Equivalent to the said process is to be considered such method of working whereby as starting materials the normal salts of the aliphatic polyhydroxy carboxylic acids with the said metals are used and these salts are transformed into the neutral complex compounds by means of alkali metal-or nitrogen bases. Of course, also the use of a water-soluble salt of the said metals simultaneously with an about corresponding quantity of an alkaline reacting base is to be considered equivalent to the use of the metal oxides or hydroxides, since in this manner of working the metal hydroxides are produced from the metal salts in statu nascendi. From these explanations it results that the succession of the addition of the metal compound and of the neutralizing base is not of decisive importance for our new process, for example, also the salts of the aliphatic polyhydroxy carboxylic acids with an alkali metal or a nitrogen base may be used as starting material. However, in each case it is essential that the final reaction of the complex compound is made about neutral. From the aqueous reaction mixture the complex compounds formed may advantageously be separated by pouring the solution into an alcohol, preferably methyl alcohol, and washing the precipitate formed with an alcohol, for example, an about 80–100% aqueous methyl alcohol.

As complex forming aliphatic polyhydroxy carboxylic acids containing at least 5 carbon atoms and at least three hydroxy groups bound to three adjoining carbon atoms we prefer to use saccharic-, gluconic- and glucoheptonic acid and, therefore, the production of complex compounds with these acids has been described in particular in the examples. However, it may be mentioned that in the same manner as the said acids also other aliphatic polyhydroxy carboxylic acids have proved operable in the present process, for example, pentonic acids, such as arabonic-, xylonic- and 2-methyl-pentane-tetrolic acid, furthermore, galactonic- or mannonic acid, mannoheptonic acid, lactobionic acid and the like, and also

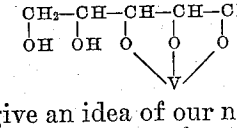
such acids are within the scope of the present invention.

In the examples mentioned below we have described the production of complex compounds with those metals which are of an especially high interest for the medicinal use in this combination, that is to say arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten. In the same manner as described in the examples water-soluble, neutral metal complex compounds of zinc, thallium, titanium, uranium, manganese, thorium and the like may be prepared, displaying a similar behaviour as the products described in the examples and being characterized by the metal used in each individual case.

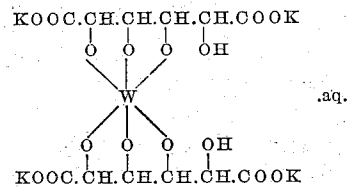
As neutralizing bases the hydroxides or carbonates of alkali metals, preferably of sodium and potassium, but also nitrogen bases, such as ammonia, methylamine, diethylamine, ethylenediamine, diethylaminoethanol, piperidine, piperazine and the like may be employed.

The composition of the new complex compounds may vary in wide limits and is not restricted to stoichiometric proportions. Moreover, particularly those compounds which do not correspond to simple atomic proportions, display often especially good therapeutic properties. In this connection it may be emphasized that the present invention does not intend to provide metal complex compounds of a clear chemical composition which would be of a more scientific interest, but it intends to provide valuable medicinal media.

In view of the complicated composition of the new products proved by analysis we are not able to give structural formulæ which would be suitable to formulate the products of the present invention in a general and more easily visible manner. However, in order to more clearly indicate which types of compounds are presumably formed by the present process the following formula of a relatively simply composed sodium vanadium-III-gluconate



may give an idea of our new products. Such products are in conformity with the properties of the new products, however, in order to produce a product displaying properties which make our new complex compounds suitable for medicinal use it is not at all required that the metal is bound to the aliphatic polyhydroxycarboxylic acid in the proportion of one gram atom to one mol as above, rather, in many cases complex compounds of other proportions have proved especially good properties, whereby the complex bound metal may be combined with the aliphatic polyhydroxy carboxylic acid in other proportions, the metal apparently being bound to the hydroxy groups of different molecules of the aliphatic polyhydroxy carboxylic acid. As an other term for the probable constitution of a potassium tunsten-saccharate may be mentioned the following formula:



That the metal is bound in the new complex compounds in complex like linkage follows from the fact that these metals are not precipitated by dilute caustic alkali lyes or dilute mineral acids.

The new compounds are white to colored powders, this depending on the metal used for the complex compounds. These compounds decompose on heating without distinctly melting and yield neutral aqueous solutions which are suitable for injection purposes in the medicinal practice.

The invention is illustrated by the following examples without being restricted thereto:

Example 1

3.5 grams of cobalt chloride are added to a solution of 12.5 grams of acid potassium saccharate ($HOOC.C_4H_8O_4.COOK$) in 60 ccs. of hot water and then dilute caustic soda lye is added till about the neutral point. By stirring the resulting solution into methyl alcohol the complex compound formed is precipitated. After separating and drying the precipitate the potassium sodium cobalt-saccharate is obtained as a lilac-red colored powder containing about 6.5% of cobalt, which dissolves in water with a neutral reaction. Caustic soda lye does not precipitate cobalt hydroxide.

By employing 5.5 grams of cobalt chloride a complex compound is obtained possessing analogous properties, but a cobalt content of about 9%.

Example 2

10 ccs. of a 50% solution of gluconic acid are diluted with 20 ccs. of water. A solution of 2 grams of vanadium trichloride in a little water is then added. The solution is then neutralized with dilute caustic soda lye. From the resulting solution the sodium vanadium-III-gluconate formed is precipitated by means of methyl alcohol, separated and dried. A greyish-green powder containing about 10% of vanadium is obtained which dissolves readily in water with a neutral reaction and a green coloration.

Example 3

6 grams of hydrated vanadium tetroxide

(containing 23% of vanadium) are dissolved in a solution of 6.2 grams of acid potassium saccharate ($HOOC.C_4H_8O_4.COOK$) in 30 ccs. of hot water. The solution is then neutralized with dilute caustic soda lye and the potassium sodium vanadium-IP-saccharate formed precipitated by stirring in methyl alcohol. After separation and drying a blue colored powder containing about 13% of vanadium is obtained, which dissolves readily in water with a blue coloration.

Example 4

A solution of 12.5 grams of acid potassium saccharate ($HOOC.C_4H_8O_4.COOK$) in 60 ccs. of hot water is mixed with 3 grams of copper chloride and approximately neutralized while hot with dilute caustic soda lye. After cooling the potassium sodium copper-saccharate formed is precipitated by stirring the solution into methyl alcohol. A light blue powder containing about 7.5% of copper is obtained after separating and drying, which dissolves readily in water with a neutral reaction. The aqueous solution is not precipitated by the addition of caustic soda lye.

When using in this example 4.4 grams of copper chloride a potassium sodium copper-saccharate is obtained containng about 11% of copper.

In an analogous manner copper complex compounds of glucoheptonic acid may be prepared.

Example 5

12.5 grams of acid potassium saccharate are dissolved in water and 10 ccs. of 5 n-caustic potash-lye. A solution of 5.5 grams of cobalt chloride is added and the cobalt salt formed precipitated by pouring the mixture into methyl alcohol. 9 grams of the acid reacting salt thus obtained are dissolved in 50 ccs. of water and mixed with 2 n-caustic potash solution until the precipitate primarily produced by the addition of the caustic potash solution just still disappears. The potassium cobalt-saccharate formed is precipitated by pouring the mixture into methyl alcohol, while stirring. It is a pink colored powder readily soluble in water with neutral reaction and contains about 10% of cobalt.

Example 6

A solution of 2 grams of lanthanum carbonate in 20 ccs. of normal hydrochloric acid and 30 ccs. of water is mixed while stirring with a solution of 2.5 grams of potassium-saccharate in 50 ccs. of water and 10 ccs. of normal caustic soda lye. On boiling the mixture a precipitate is produced; it is filtered with suction, washed with water, methyl alcohol and ether and dried. 2 grams of the product thus obtained are made into a paste with 10 ccs. of water. The paste is dissolved in normal caustic soda lye to a neutrally reacting solution and the solution is poured into methyl alcohol. After separating and drying the precipitate formed the sodium-lanthanum-saccharate is obtained as a white powder containing about 30% of lanthanum and being readily soluble in water.

Example 7

12 grams of tungstic acid are dissolved in 40 ccs. of water and 10 ccs. of 5 n-caustic potash solution while heating. The solution is mixed with 25 grams of acid potassium saccharate which dissolves on heating. The solution is neutralized by the addition of 5 n-caustic potash solution, filtered and the complex salt formed precipitated by pouring into methyl alcohol. After separating the precipitate and drying, the potassium tungsten-saccharate is obtained as a whitish powder containing about 19% of tungsten and being readily soluble in water with neutral reaction.

Example 8

7 grams of molybdic acid are dissolved in a solution of 12.5 grams of acid potassium saccharate and 50 ccs. of water while adding 2 n-caustic potash solution until the reaction is neutral. The solution is filtered and the filtrate is evaporated to dryness. The residue of potassium molybdenum-saccharate is after powdering a weakly colored powder readily soluble in water with neutral reaction.

Example 9

50 ccs. of 2 n-gluconic acid are mixed with an aqueous solution of 11 grams of stannous chloride. The solution is neutralized with 5 normal caustic soda lye filtered and poured into methyl alcohol while stirring. After separating and drying the precipitate the sodium tin-gluconate is obtained as a whitish powder readily soluble in water.

Example 10

6 grams of 50% gluconic acid and 2.46 grams of cerous chloride are dissolved in about 20 ccs. of water. The solution is neutralized with caustic soda lye and poured into methyl alcohol while stirring. The precipitate formed is separated off and dried. The sodium cerium-gluconate is obtained as a yellowish powder containing about 30% of cerium and being readily soluble in water.

Example 11

10 grams of cerium-saccharate (obtainable by reacting upon cerous chloride with potassium sodium-saccharate) are made into a paste with 30 ccs. of water. The paste is dissolved by the addition of an aqueous 5 normal diethylamine solution, the solution is filtered and poured into acetone while stirring. The diethylamine cerium-saccharate

is a light yellow powder containing about 24% of cerium and being readily soluble in water.

Example 12

A solution of 5 grams of acid potassium-saccharate in 20 ccs. of normal caustic soda lye is boiled with 4 grams of arsenic anhydride until the latter has almost dissolved. The solution is neutralized with a few drops of 5 normal caustic soda lye and poured into methyl alcohol while stirring. The potassium sodium arsenic-saccharate obtained is a powder readily soluble in water.

We claim:—

1. As new products complex compounds of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, with an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms, said complex compounds having been neutralized with a base of the group consisting of alkali metal bases and aliphatic amines, being whitish or colored powders, soluble in water with about neutral reaction.

2. As new products complex compounds of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, with an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms, said complex compounds having been neutralized with a base of the group consisting of alkali metal bases and aliphatic amines, being whitish or colored powders, soluble in water with about neutral reaction.

3. As new products complex compounds of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, with an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic-acid, said complex compounds having been neutralized with a base of the group consisting of alkali metal bases and aliphatic amines, being whitish or colored powders, soluble in water with about neutral reaction.

4. As new products complex compounds of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten with an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic-acid, said complex compounds having been neutralized with a base of the group consisting of alkali metal bases and aliphatic amines, being whitish or colored powders, soluble in water with about neutral reaction.

5. As new products complex compounds of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, with an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms, said complex compounds having been neutralized with an alkali metal base of the group consisting of sodium and potassium, being whitish or colored powders, soluble in water with about neutral reaction.

6. As new products complex compounds of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, with an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms, said complex compounds having been neutralized with an alkali metal base of the group consisting of sodium and potassium, being whitish or colored powders, soluble in water with about neutral reaction.

7. As new products complex compounds of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, with an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, said complex compounds having been neutralized with an alkali metal base of the group consisting of sodium and potassium, being whitish or colored powders, soluble in water with about neutral reaction.

8. As new products complex compounds of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, with an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, said complex compounds having been neutralized with an alkali metal base of the group consisting of sodium and potassium, being whitish or colored powders, soluble in water with about neutral reaction.

9. As new products complex compounds of copper with an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, said complex compound having been neutralized with sodium hydroxide, being blue powders, soluble in water with about neutral reaction.

10. As a new product sodium potassium copper-saccharate, being a blue powder, containing about 11% of copper, being soluble in water with about neutral reaction.

11. The process which comprises reacting upon an aliphatic polydydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms with a metal oxygen compound of the group consisting of

oxides and hydroxides of a metal other than antimony, iron, alkali- and alkaline-earth metals, but having an atomic number higher than 21, in aqueous solution and adding a base of the group consisting of alkali metal bases and aliphatic amines, in an amount sufficient to form the neutral complex compound.

12. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms with a metal oxygen compound of the group consisting of oxides and hydroxides of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, in aqueous solution and adding a base of the group consisting of alkali metal bases and aliphatic amines, in an amount sufficient to form the neutral complex compound.

13. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, with a metal oxygen compound of the group consisting of oxides and hydroxides of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, in aqueous solution and adding a base of the group consisting of alkali metal bases and aliphatic amines, in an amount sufficient to form the neutral complex compound.

14. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, with a metal oxygen compound of the group consisting of oxides and hydroxides of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, in aqueous solution and adding a base of the group consisting of alkali metal bases and aliphatic amines, in an amount sufficient to form the neutral complex compound.

15. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms with a metal oxygen compound of the group consisting of oxides and hydroxides of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, in aqueous solution and adding a base of the group consisting of sodium and potassium hydroxide in an amount sufficient to form the neutral complex compound.

16. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of at least 5 carbon atoms and containing at least three hydroxy groups bound to three adjoining carbon atoms with a metal oxygen compound of the group consisting of oxides and hydroxides of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, in aqueous solution and adding a base of the group consisting of sodium and potassium hydroxide in an amount sufficient to form the neutral complex compound.

17. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, with a metal oxygen compound of the group consisting of oxides and hydroxides of a metal other than iron, antimony, alkali- and alkaline-earth metals, but having an atomic number higher than 21, in aqueous solution and adding a base of the group consisting of sodium and potassium hydroxide in an amount sufficient to form the neutral complex compound.

18. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, with a metal oxygen compound of the group consisting of oxides and hydroxides of a heavy metal of the group consisting of arsenic, copper, vanadium, tin, cerium, molybdenum, cobalt, lanthanum and tungsten, in aqueous solution and adding a base of the group consisting of sodium and potassium hydroxide in an amount sufficient to form the neutral complex compound.

19. The process which comprises reacting upon an aliphatic polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, with a metal oxygen compound of the group consisting of oxides and hydroxides of copper in aqueous solution and adding sodium hydroxide in an amount sufficient to form the neutral complex compound.

20. The process which comprises reacting upon saccharic acid in form of its acid potassium salt with copper hydroxide in statu nascendi and adding sodium hydroxide in an amount sufficient to form the neutral complex compound.

21. The process which comprises reacting upon 12.5 parts by weight of saccharic acid in form of its acid potassium salt with 4.4 parts by weight of copper chloride in aqueous solution and adding sodium hydroxide in an amount sufficient to form the neutral complex compound.

22. As new products complex compounds of tin with a polyhydroxy carboxylic acid of the group consisting of saccharic-, gluconic- and glucoheptonic acid, said complex compounds having been neutralized with sodium hydroxide, being whitish powders, soluble in water with about neutral reaction.

23. As a new product sodium-tin-gluconate, being a whitish powder, being soluble in water with about neutral reaction.

In testimony whereof, we affix our signatures.

HANS SCHMIDT.
HEINRICH JUNG.