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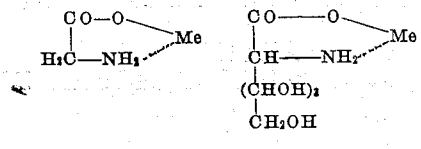
COMPLEX GLUCOSAMINIC ACID SALTS OF THE METALS OF THE IRON GROUP

No Drawing. Application filed November 5, 1931, Serial No. 573,298, and in Germany November 10, 1930.

The present invention relates to the preparation of complex glucosaminic acid salts of the metals of the iron group which possess valuable therapeutical properties.

It is known that the derivatives of metals in order that they can be used in the therapy, must possess some special properties, such as for example a small toxicity, a good toleration on injection and a sufficient solubility. The first two properties depend on the chemical constitution of the compound, which for this purpose must possess a neutral character and in which the metal must be linked in a complex manner, whereas the solubility in water generally depends on the presence of an acid group which is neutralized with an alkali metal or on the presence of several hydroxylic groups in the molecule.

It has now been found, that the glucosaminic acid yields such metal salts, that completely fulfil the above cited requirements. They are very stable and contain probably a five ring, as shown by the following formulæ, like the heavy metal salts of other amino acids, e. g. the copper salt of glycocoll (see P. Pfeiffer "Organische Molekülverbindungen", 1922, page 176):



The capacity for the formation of complex compounds is further increased by the presence of the alcoholic hydroxylic groups contained in the molecule of the glucosaminic acid, as it is well known that the polyoxycarboxylic acids such as tartaric acid give complex metal compounds. The metal compounds of the glucosaminic acid, containing in their molecule besides one amino group several hydroxylic groups possess a much better stability of the metal complex, produce a smaller irritation of the tissues on injection and are much better tolerated, in comparison with metal compounds of the oxy- and polyoxy-carboxylic acids that do not contain an amino group. As compared to the complex heavy metal salts of the usual aminoacids which contain no or only one hydroxylic group and which owing to their bad solubility present no interest for therapeutical purposes, the new compounds prepared according to the present process possess quite a sufficient solubility for the therapeutical application and may, therefore be successfully used.

According to the literature, some normal metal salts of the glucosaminic acid, such as the copper, zinc and silver salts have already been prepared for the purpose of characterizing this acid (see E. Fischer & F. Thiemann, Ber. 27, page 144, 1894). But from this publication it could not at all be foreseen, that the glucosaminic acid would yield with other metals therapeutically valuable and complex compounds, for the reason, that the described copper salt is insoluble in water and the silver salt is unstable and is decomposed under reduction to the metal.

For the preparation of the new compounds several methods may be used.

By treating the glucosaminic acid with oxides or hydroxides of the metals the new compounds may be obtained. The same result is reached if an equivalent quantity of an organic or an inorganic base is added to a solution containing the glucosaminic acid and the heavy metal salt, whereby the metal hydroxide obtained in statu nascendi reacts with the glucosaminic acid. In the case where the sulphates of the heavy metals are used it is indicated to employ barium hydroxide, because the precipitated barium sulphate can easily be separated from the solution. By using the metal chlorides, it is preferable to produce the metal hydroxides by means of an addition of diethylamine or of similar bases, the chlorides of which are soluble in alcohol and may therefore be easily separated from the metal salts of the glucosaminic acid which are insoluble therein.

It is further also possible to treat an aqueous solution of the glucosaminic acid with a carbonate of a heavy metal, whereby the carbonate is dissolved under production of carbon dioxide, although the glucosaminic

acid owing to its intramolecular salt formation possesses a neutral reaction.

The new salts may also be obtained by double reaction between the salts of the glucosaminic acid and heavy metal salts, such as between the barium salt of the glucosaminic acid and a sulphate of a heavy metal. It is possible to prepare besides the normal salts which correspond to the valency of the metals and which are generally well crystallized, also such compounds of the glucosaminic acid that contain two, three or several times more of a metal than corresponds to the normal stochiometric proportion. Such salts are distinguished by a good solubility.

The heavy metal salts of the glucosaminic acid do not yield with alkali or with other basic compounds a precipitation of the heavy metal hydroxide, but they give the easily soluble double salts of heavy metal and alkali metal or aminosalts of the glucosaminic acid.

The new process is illustrated by the following examples, which are not limitative, the parts being by weight.

Example 1

To a solution of 1 part of glucosaminic acid in 20 parts of water is added at 95° C. 1 part of nickel carbonate, whereby carbon dioxide escapes and the solution becomes blue. After 10 minutes the solution is separated from the excess of nickel carbonate by filtration and the hot filtrate obtained is diluted with 10 parts of hot alcohol of 95%. The crystallization of nickel glucosaminate begins immediately. Pale blue crystals of the composition $(C_6H_{12}O_6N)_2Ni$ containing 12.96% of Ni (theor. 13.1%) are obtained. By dissolving one molecule of nickel glucosaminate in one molecule of a 2-n-sodium hydroxide solution a dark blue solution is obtained from which the nickel-sodiumglucosaminate of the composition

$$[(C_6H_{12}O_6N)_2Ni]Na$$

is precipitated by means of absolute alcohol.

By dissolving one molecule of nickelglucosaminate in 2 molecules of sodium hydroxide an intensively green colored nickel glucosaminate is obtained.

Example 2

To a solution of 1 part of glucosaminic acid in 20 parts of water is added at 95° C. one part of cobalt carbonate, whereby carbon dioxide escapes and the solution becomes colored to deep wine-red. After 30 minutes the solution is filtered and the filtrate introduced into 100 parts of absolute alcohol. The very easily soluble cobalt glucosaminate is obtained in form of a wine-red powder of the composition $(C_6H_{12}O_6N)_2Co$.

By working as described in Example 1 the respective cobalt-alkalimetalglucosaminates may be prepared.

Example 3

A concentrated aqueous solution containing one molecule of glucosaminic acid and one molecule of ferric chloride is treated with 3 molecules of diethylamine, whereby the solution becomes colored in a deep brown-red shade. By introducing this solution into absolute alcohol the iron glucosaminate is precipitated in form of rusty-brown flocks. The product thus obtained contains generally traces of chlorine. In order to separate them, the salt is again dissolved in a small quantity of water and reprecipitated by introducing the aqueous solution into alcohol containing a small amount of diethylamine and eventually a certain quantity of ether. A rusty-brown powder of the composition $C_6H_{10}O_6NFe$ is obtained in this manner. It contains 23.1% of Fe (theor. 22.5%).

By replacing the ferric chloride by a salt of the bivalent iron, a similar complex salt is obtained. Its aqueous solutions are dark green, but change the color on oxidation by air.

Similar salts may also be prepared from salts of the bivalent and trivalent manganese salts. They are also soluble in water with a brown coloration and yield stable aqueous solutions.

What we claim is:

The complex glucosaminic acid salts of the iron group, prepared by interaction of the glucosaminic acid with salts of the metals of the iron group, which constitute in dry state nonhygroscopic powders, soluble in water, yielding stable solutions and which give with basic compounds easily soluble salts.

In witness whereof we have hereunto signed our names this 27th day of October, 1931.

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