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PREPARATION AND PROPERTIES OF CALCIUM LACTOBIONATE-CALCIUM BROMIDE

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ABSTRACT

The double salt of calcium lactobionate and calcium bromide, which was prepared for the first time at the National Bureau of Standards, gives promise of becoming an important medicinal agent. According to clinical tests published in foreign journals, its sedative action is almost twice that which corresponds to its bromine content, and when administered in effective quantity it does not cause "bromide rashes" such as frequently develop when alkali bromides are used. The prevalence in the United States of neurasthenia and similar ailments which require sedatives of various types should afford a lucrative market for this salt. The simple process for its manufacture reported in this paper should make it available to all for the alleviation of suffering and distress.

CONTENTS

I. MEDICAL ACTION AND USE OF CALCIUM LACTOBIONATE-CALCIUM BROMIDE

In the 1887 edition of the National Dispensatory[1] it was pointed out that calcium bromide "produces the characteristic effects of the bromides more promptly than the analogous compounds, and also induces sleep where they failed to do so." It was also mentioned that calcium bromide is supposedly "peculiarly appropriate for relieving the *insomnia* caused by mental labor or excitement, and the exhausted and irritable states of the nervous system, accompanied by headache, vertigo, insomnia, and extreme mental excitability", and that it "cured epilepsy in very young infants when bromide of potassium failed." In spite of these statements calcium bromide has failed to gain much support from the medical profession, possibly because it is very deliquescent and has a pungent, bitter, disagreeable taste.

In 1927 a double salt of calcium lactobionate and calcium chloride was described in a patent issued to Stoll and Kussmal.[2] At that time the writer was working with C. S. Hudson on the oxidation of aldoses and had on hand some amorphous calcium lactobionate from which he prepared a new crystalline calcium bromide salt analogous to the calcium chloride salt of Stoll and Kussmal. In marked contrast to calcium bromide the new salt is not hygroscopic and may be kept indefinitely without appreciable deterioration. Moreover, it has a

[1] 4th edition, p. 350 (1887).
[2] U. S. Patent 1648368 (Nov. 8, 1927).

mild taste which is much less disagreeable than that of the widely used sodium, potassium, and ammonium bromides.

These facts, together with the knowledge that the calcium salts of the sugar acids, as well as calcium bromide, have sedative properties, led the writer to believe that the new salt had sufficient therapeutic value to justify obtaining a public service patent.

The application which was filed and assigned to the United States Government became involved in interference with an application filed by Stoll and Burckhardt. The testimony which was introduced during the interference indicates that subsequent to the preparation of the salt in this country it was prepared by Stoll and Burckhardt in Switzerland and subjected to numerous clinical tests. As has been anticipated, the new salt proved to have valuable therapeutic properties. Administration of the compound in 67 cases is reported by W. Winterseel [3] in an article entitled Kombinierte Brom-Calciumbehandlung mit Calcibromat (Sandoz); and 47 cases are given by E. Blum [4] in an article entitled Klinische Erfahrungen ueber eigenartige synergistische Brom-Kalzium-Wirkung in der Neurologie.

The clinical tests described in these articles indicate that the compound is useful in the treatment of epilepsy, hyperthyroidism, neurasthenia, nervous heart, and other similar ailments. Of particular importance, however, is the fact that the sedative action is much greater than one might anticipate from its bromide content. Thus, it is possible to obtain good results without using sufficient bromide to cause "bromide rashes"; and it is reported that in cases which had been previously treated with "triple bromide" and had developed rashes, these cleared up when calcium lactobionate-calcium bromide was used in place of the triple bromide. These promising results should stimulate interest and clinical investigations of the use of the compound in this country.

II. PREPARATION OF CALCIUM LACTOBIONATE-CALCIUM BROMIDE

Although the simplest method for the preparation of calcium lactobionate-calcium bromide consists in oxidizing lactose with bromine water in the presence of calcium carbonate. followed by crystallization of the double salt from the resulting solution, this method is not economical because only half of the bromine is converted into the double salt. This objectionable feature can be eliminated by combining the bromine oxidation with the electrolytic oxidation [5] which was worked out at the National Bureau of Standards. The procedure is essentially the same as in the manufacture of calcium gluconate,[6] except that one equivalent of bromine is added and 1 faraday of electricity is used for each equivalent of lactose. If desired the cells can be operated in continuous manner, in which case lactose, calcium carbonate, and bromine are added, while calcium lactobionate-calcium bromide is crystallized from the electrolyzed solution. In

[3] Medizinische Klinik, no. 7, p. 236. (Published by Urban and Schwarzenberg, Berlin, 1934.)
[4] Schweiz. med. Wochschr. 63, 446 (1933).
[5] Isbell, U. S. Patent 1976731 (Oct. 16, 1934).
[6] Isbell, Frush, and Bates, BS J. Research 8, 571 (1932) RP436.

small-scale operations it is generally more convenient to add the lactose, bromine, and calcium carbonate in batches rather than continuously and to separate the product from time to time.

To avoid the handling of bromine the process can be conducted equally satisfactorily by adding calcium bromide in place of bromine, and by using 2 faradays of electricity. For commercial use, however, bromine is preferable because it is cheaper.

The following procedure has been found to give consistently satisfactory results: 1 kg of precipitated calcium carbonate and 3.6 kg of lactose (hydrate) dissolved in 10 liters of water are placed in a 20-liter crock equipped with a mechanical stirrer and 8 graphite electrodes 3 dm long and 2.3 cm in diameter. While the solution is stirred vigorously, 0.8 kg of bromine is added. Considerable foaming occurs which can be controlled by adding a few milliliters of *n*-butyl or of hexyl alcohol. After the bromine has been added and the evolution of carbon dioxide has subsided, a direct current of 10 amperes is passed through the solution, using alternate electrodes as anodes and cathodes. When the electrodes are immersed 2 dm in the solution, 6 volts are required and the current density is about 1.7 amp/dm^2 of anode surface. The current density may be varied over a wide range without materially reducing the efficiency. After about 28 hours when all of the sugar has been oxidized the electric current is stopped, but stirring is continued until the evolution of carbon dioxide ceases, in order that any lactobionic lactone may be converted into calcium lactobionate. After filtration the electrolyzed solution is concentrated under reduced pressure to a sirup from which nearly pure calcium lactobionate-calcium bromide crystallizes. The crystals can be grown in the evaporating pan while concentration is taking place, in a manner similar to the "graining" of sugar. The resulting crystalline product is separated from the mother liquor by means of a centrifugal machine and washed with a high-purity calcium lactobionate-calcium bromide sirup. The mother liquors are ordinarily returned to the electrolytic cell and worked up with the following batch. Yields of over 90 percent are usually obtained.

If desired the product can be purified by dissolving it in hot water and adding several volumes of alcohol, whereupon the salt crystallizes in good yield. But usually it is preferable to crystallize the product from hot water in the following manner: Three parts of the salt are dissolved in two parts of boiling water. A small quantity of decolorizing carbon is added and the solution is filtered and seeded with powdered crystalline calcium lactobionate-calcium bromide. By constant agitation and slow cooling large crystals are obtained which are collected on a filter and washed, first with a small quantity of water saturated with calcium lactobionate-calcium bromide, and finally with aqueous alcohol containing approximately equal volumes of alcohol and water. The product after drying at 50° C corresponds to the following analysis: Calculated for $Ca(C_{12}H_{21}O_{12})_2\ CaBr_2.6H_2O$: Ca, 7.54; Br, 15.04. *Found:* Ca, 7.57; Br, 14.95. An aqueous solution containing 7.3 g per 100 ml gives $[\alpha]_D^{20}=+18.7$. A saturated solution of the hydrated salt at 20° C contains 31.5 percent, by weight, and has a density of 1.183 g per milliliter. It crystallizes in hexagonal prisms which have six rectangular faces.

III. USE OF CALCIUM LACTOBIONATE-CALCIUM BROMIDE IN THE MANUFACTURE OF CALCIUM LACTOBIONATE

Because calcium lactobionate crystallizes in hair-like crystals [7] which are difficult to separate from the mother liquor, it is necessary to use an intermediate salt for separating it from the unoxidized sugar and other impurities.

In their process for the preparation of calcium lactobionate by the electrolytic oxidation of lactose, Isbell and Frush [8] employed the basic calcium salt previously prepared by Hudson and Isbell.[9] The use of this basic salt is objectionable because the accompanying strongly alkaline solution causes severe decomposition of any unoxidized

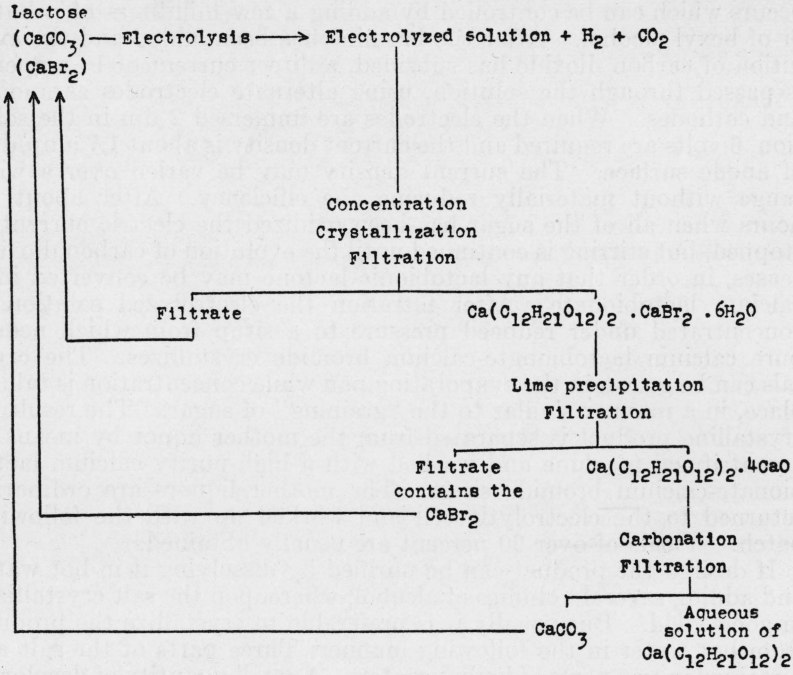

FIGURE 1.

sugar, and thus prevents the satisfactory operation of a continuous process such as that employed in the manufacture of calcium gluconate.[10] By using the calcium bromide double salt in conjunction with the basic calcium salt, the action of alkali on any unoxidized sugar is avoided and the method of manufacture of calcium lactobionate thereby improved.

Equivalent quantities of lactose, calcium carbonate, and calcium bromide are placed in the electrolytic cell and the oxidation is conducted as in the manufacture of calcium gluconate. From time to time crops of crystalline calcium lactobionate-calcium bromide are separated and treated with hydrated lime to give basic calcium

[7] Isbell, BS J. Research **11,** 713 (1933) RP618.
[8] BS J. Research **6,** 1145 (1931) RP328.
[9] BS J. Research **3,** 59 (1929) RP82.
[10] Isbell, Frush, and Bates, BS J. Research **8,** 571 (1932) RP436.

lactobionate and calcium bromide. After separating the basic calcium lactobionate by filtration, the filtrate containing calcium bromide is returned to the electrolytic cell, together with additional lactose and calcium carbonate, and the process continued.

The basic calcium lactobionate is converted into the normal salt by carbonation, giving as a byproduct calcium carbonate, a part of which can be returned to the electrolytic cell. As may be seen from the diagram, lactose and lime are the only raw materials consumed. There is some loss of bromine and occasionally the electrolyte becomes foul and must be discarded and the bromide reclaimed.

The essential features of the process outlined above have been covered by U. S. Patent 1 980 996, which is assigned to the Government of the United States.[11] Figure 1 illustrates the continuity of the various steps in the process.

[11] Anyone desiring to use either patent 1 980 996 or 1 976 731 should make application to the Secretary of Commerce for a license.

WASHINGTON, September 3, 1936