

THE STATE OF SILVER IN PROTARGOL (ARGENTI PROTEINATUM)
AND COLLARGOL (COLLOID SILVER; ARGENTUM CRÉDÉ).*BY I. M. KOLTHOFF.¹

I. The use of silver nitrate (*stone of hell; lapis infernalis*) has been well known in medicine for a long time. There are, however, several objections against its application; for example, it is reduced in the body to metallic silver, which is deposited, especially, in the cells of the skin. The consequence of this is that the latter becomes blackened, giving the patient a dark appearance. This black color, called argyria, may last for years, even during the whole life of the individual affected. The color may even be so intensely black that the patient resembles a negro. Th. Paul refers to the case of a clergyman in the army who was treated for such a long time with silver nitrate that coloration became so complete that the Queen of Sweden, observing the man, asked in astonishment, why a negro had been appointed as a clergyman?

After Lister had discovered the antiseptic treatment of wounds, silver solutions were applied for that purpose, especially to the infected mucous membranes. The silver nitrate solutions appeared to irritate the tissues in a very disagreeable way, hence the endeavor to prepare difficultly soluble or complex silver preparations. It was not until 1894 that Schering succeeded in preparing a silver compound of this kind, which was marketed under the name of Argentamine; it contains silver phosphate in aqueous solution of diethylenediamine and is still used in the treatment of gonorrhœa. In the same year (1894) Heyden in Radebeul (near Dresden) prepared the well-known Collargol, which contains the silver in a colloidal state. It is also called colloidal silver or Argentum Crédé, as Crédé was the first to point out how to prepare this colloidal silver.

In 1895 Argonin, a silver caseinate compound, was recommended for the treatment of gonorrhœa; and at last, in 1897, Friedrich Bayer & Co. prepared the well-known Protargol—Argenti proteinatum. According to the description by this Company, it is a silver-proteid compound with a silver content of 8.3 per cent. The great advantage of this preparation is, that it has no irritating action and a concentrated solution can be prepared of it (50 per cent.). Since then a great many colloidal silver preparations have been put on the market; Th. Paul² in 1912 gave a list of 52 silver preparations used in medicine, and since that time this number has increased very rapidly. During the last few years preparations have been employed in which the silver occurs in the presence of other metals.

II. A very interesting investigation relative to the action and the properties of colloidal silver preparations has been carried out by Theodor Paul.² Some of the results of his researches are as follows:

A. The bactericidal potency depends on the magnitude of the silver-ion concentration of the solution and its ability to split off new silver ions, when the latter are removed in any way. So if we express this action in modern terms, we could say that the bactericidal potency depends on the buffer-action of the preparation for silver ions.

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² Th. Paul, *Z. Elektrochem*, 18, 521 (1912).

B. The preparations or their solutions must produce mixtures with the organic tissue liquids and aqueous solutions of proteids, bases and acids, and should not give precipitates with them.

C. The silver-protein compounds are more soluble than silver chloride, by an excess of sodium chloride they are transformed into silver chloride.

D. In diluting the colloidal silver preparations we may distinguish three cases:

a. The silver-ion concentration decreases. This is the case with Protargol. A 1 per cent. solution has a silver-ion concentration of 8×10^{-3} , a 0.31% solution of 1×10^{-3} .

b. The silver-ion concentration remains constant. This is the case with Sophol, the solution of which has a (Ag') of 2×10^{-5} .

c. The silver-ion concentration increases. Such is the case with Collargol, Argentamin, Lysargin. A 4-per cent. Collargol solution has a (Ag') of 1×10^{-4} ; a 0.25 per cent. solution of 2×10^{-3} .

I wish to remark here that it was possible for me to confirm Paul's statement about the Protargol, but not relative to Collargol, as I will show later.

According to my opinion and experience, it is not quite certain that the bactericidal potency only depends on the magnitude of the silver-ion concentration, as Paul and Krönig concluded from their well-known investigation. In working with colloidal solutions, it may be expected that this bactericidal action also largely depends on the fineness of the silver particles, so that finely dispersed suspensions of silver chloride, bromide and iodide also may have a good action. Some preliminary experiments carried out in our laboratory confirmed our expectations in this respect. From a bacteriological point of view this matter is important enough to be investigated thoroughly.

III. The accurate composition of Protargol and the method of preparing it are not well known. H. V. Arny¹ states in his well-known book, "Principles of Pharmacy:" "Commercial products are usually prepared containing small amounts of proteids; such compounds having been found to yield more stable solutions. Among the proprietary forms of colloidal silver may be cited protargol and argyrol. These are now largely used in the form of glycerinic solutions for throat troubles." (The application in the treatment of gonorrhoea also may be mentioned.) Neither Schmidt ("Lehrbuch der pharm. Chemie," 1919) nor Hager gives satisfactory information about these preparations.

Only S. Fränkel² informs us that Protargol is obtained by precipitating a peptone solution with silver nitrate. The precipitate is warmed with protalbus and the solution evaporated to dryness. Though the prescription is very vague, we succeeded in our laboratory in obtaining good preparations of Protargol.

The silver proteinate may also be prepared by the action of moist silver oxide on albumoses.

From the above it may be concluded that the silver in Protargol is not present in the metallic state, but that it is in some way (chemical and colloidal) combined with proteids. This is not the case with Collargol, which is practically metallic silver in a colloidal state. It is prepared by adding silver nitrate to a solution of

¹ H. V. Arny, "Principles of Pharmacy," second edition, 1920, p. 565.

² S. Fränkel, "Arzneimittelsynthese," 1919.

ferrous sulphate, sodium citrate and sodium carbonate. A brown precipitate containing 97 per cent. of silver results and this, after washing free from impurities with ammonium citrate solution, is soluble in water or 10 per cent. sodium chloride solution. In all probability it contains a little gelatin as a protecting colloid. According to the data given in the literature, the silver content ranges between 75 and 98 per cent.

IV. The Protargol used by me was an original preparation of Bayer. The water content is not easy to determine, as the dried substance is very hygroscopic and the residue loses its last traces of water very slowly. We found a water content of 9.87 per cent. (after drying for 35 hours), which is a higher proportion than most pharmacopœias allow. According to the description of Bayer and most pharmacopœias the soluble silver content is stated to be between 8 and 9 per cent. (refers to the dried substance). We, however, found in the original substance a soluble silver content of 7.08 per cent., corresponding to 7.77 per cent. in the dried substance. The total silver content, however, was higher and appeared to be as high as 7.87 per cent. corresponding to 8.65 per cent. in the dried substance. In contradiction to the description given in Bayer's papers and in different pharmacopœias, I found that the original preparations all contain silver chloride. From the above could be concluded that the dry preparation used by me contained $(8.65-7.77) = 0.88$ per cent. silver as silver chloride. In order to check these results, we determined the silver in the insoluble residue that remained after the treatment with nitric acid and washing out with water.

In agreement with the above result we found, by means of direct analysis, a quantity of silver present as silver chloride corresponding to 0.85 per cent. Hence, it seems to me that the pharmacopœias must admit a definite amount of chloride in Protargol.

We have also determined the *N*-content of the Protargol; it contained 13.8 per cent. in the original substance, or 15.2 per cent. in the water-free substance. It is very peculiar that in carrying out the destruction with sulphuric acid without a catalyzer, the liquid soon becomes clear and colorless. In our determination this was the case after two hours, but the destruction was not complete, as all nitrogen was not present in the ammonium state. When the distillation was carried out after a destruction of two hours, we found the *N*-content 1 per cent. too low.

The Collargol used by us was a common commercial preparation. It contained no more than 67 per cent. silver, while 4.8 per cent. was present in the halide state.

V. As the magnitude of the silver-ion concentration seems to be of value in connection with its action as a remedy, I determined this concentration by means of a potentiometric measurement with a silver electrode. In the following table the data are given. The measurements are carried out with solutions of Protargol and Collargol:

Protargol. Concentration Protargol in per cent.	Silver-ion concentration.	Collargol. Concentration Collargol in per cent.	Silver-ion concentration.
1.4	2.9×10^{-3}	1	3.1×10^{-4}
1.0	2.8×10^{-3}	0.5	2.4×10^{-4}
0.5	2.0×10^{-3}	0.25	1.7×10^{-4}
0.25	1.2×10^{-3}	0.1	1.15×10^{-4}
0.1	0.55×10^{-3}

The silver-ion concentration in protargol is about 10 times greater than in collargol solutions of the same concentration. I suppose that in Protargol the ionic silver will have the therapeutic effect, while in Collargol the metallic silver will have this action.

In Fig. 1 we represent our results in a graph. The abscissas represent the concentration of Protargol or Collargol, and the ordinates the silver-ion exponent p_{Ag} , that is, the negative logarithm of the silver-ion concentration.

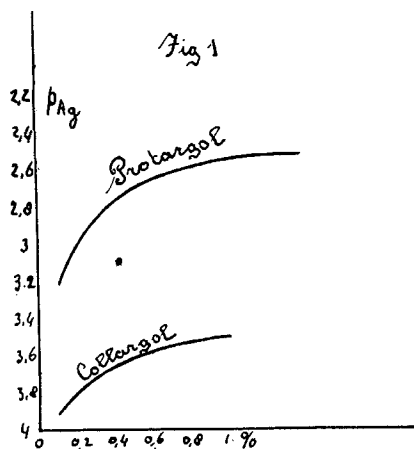


Fig. 1.

The "British Pharmaceutical Codex"¹ remarks: "The fact that solutions of silver proteinate are not precipitated by sodium chloride indicates that silver ions are not present, and any silver action can therefore result only after decomposition of the salt." From the above it is evident that this conclusion is not warranted; and as we will state in the next part, silver proteinate will react with halides, forming the corresponding silver salt. Due to the presence of the protecting colloids, these silver halides formed remain in colloidal solution, so that it gives the impression that no action occurs at all.

VI. In order to investigate whether all the silver in Protargol may be transformed into silver halides by treatment with halide solutions, we titrated solutions of silver proteinate with alkali-halides and measured the change of the silver-ion concentration during the titration by means of a silver electrode. Hence we made an application of the so-called "potentiometric titrations." I cannot enter into details about this method and must refer to preceding communications² concerning the performance of such a determination. Before I give the results of the determinations, I might refer to the variation in the silver-ion concentration in titrating an approximately 0.003 *N* silver-nitrate solution with 0.01 *N* solutions of alkali chloride, bromide and iodide respectively. In the graphs in Fig. 2 the left ordinate represents the values of "a" read on the slide wire, after the system was balanced and the right ordinate gives the corresponding silver-ion exponent p_{Ag} , *i. e.*, the negative logarithm of the silver-ion concentration, so

$$p_{Ag} = -\log (Ag^+).$$

The abscissa gives the amount of reagent added. For the sake of clearness the abscissa is shifted in the titration with chloride 3 cc. to the right, and in titration with bromide 1 cc. to the right, so that the different curves cannot coincide.

In Fig. 2, the rise in potential is the greatest in titrating with iodide, as the silver iodide is the least soluble of the three silver halides; the jump is smaller in titrating with bromide and it is the smallest in the titration with chloride.

Now we proceeded to the titration of Protargol solutions in neutral and acid mediums. As the best results were obtained in the presence of sulphuric acid, I

¹ "British Pharmaceutical Codex," 1911; p. 148.

² Published in *Rec. Trav. Chim.* 1919 up-to-date, where reference is made to other literature.

give, in Fig. 3 only the curves obtained in the presence of this acid. Fifty cc. of a 1 per cent. Protargol solution were mixed with 5 cc. 4 N sulphuric acid and titrated with 0.01 N sodium chloride, 0.01 N potassium bromide, and 0.01 N potassium iodide respectively.

Figure 3.—Though the liquids remained perfectly clear during the titrations, it is evident from the variation of the silver-ion concentration that all the silver is transformed into the corresponding silver halide. In the titration with chloride the rise in the potential is not great. From this may be concluded that the solubility of the silver proteinate is a little greater than that of silver chloride. After the addition of the amount of chloride corresponding to the quantity of silver present in

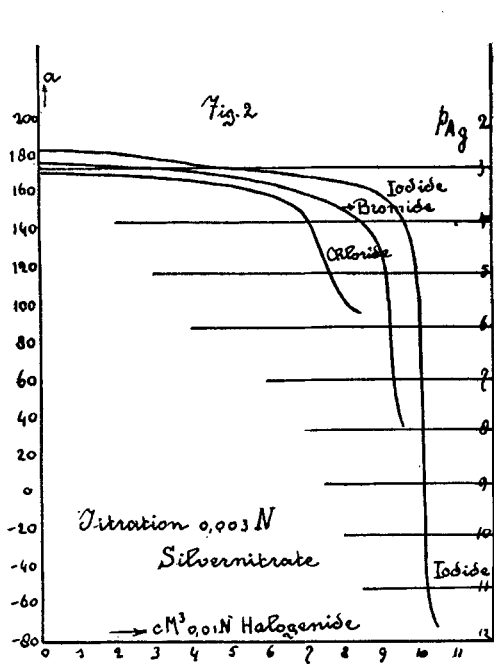


Fig. 2.

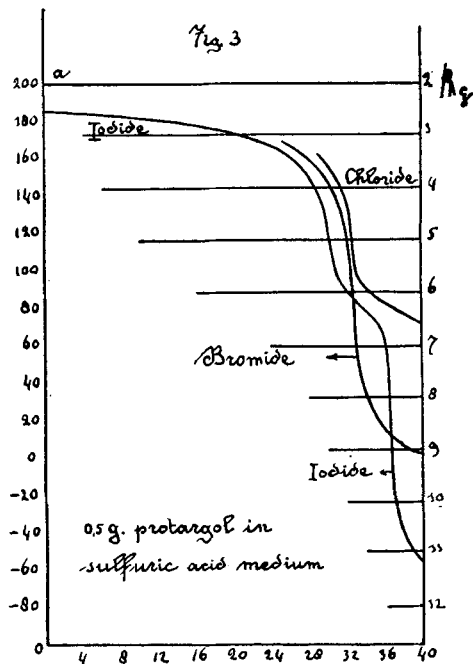
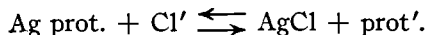


Fig. 3.

the protargol, all the silver is not completely transformed into silver chloride, but there is an equilibrium represented by the equation.



In the presence of acid this equilibrium is shifted to the right.

Hence, we have at the equivalent point silver proteinate in the presence of a large excess of silver chloride. When an excess of chloride is added, all the silver is transformed into silver chloride.

In titrating with bromide, the rise in potential is greater than is the case with chloride, but it occurs at the same place. In the titration with iodide, two jumps occur, the first corresponding to that obtained with the two other halide solutions. At that point, all the silver of the Protargol is transformed into silver halide. We found that 0.5 Gm. Protargol bound 32.75 cc. 0.01 N halide solution, corresponding to a content of 7.08% silver.

The second rise in the titration with iodide occurs after the transformation of the silver chloride—present in the Protargol—into silver iodide.



We found that 0.5 Gm. Protargol took $(36.6 - 32.75) = 3.85$ cc. 0.01 *N* iodide solution for the transformation of the silver chloride in iodide. This corresponds to a content of 0.83% silver in the state of silver chloride. By means of this potentiometric titration we found a total silver content of $7.08 + 0.83 = 7.91\%$, and 0.83% silver as chloride. This agrees very well with the results found according to the usual method of analysis communicated above, by which we found a total silver content of 7.87% and 0.79% silver as silver chloride.

I wish to emphasize that we can apply here with great advantage the potentiometric titration, as it is possible to determine by one simple titration with a standardized iodide solution the total silver content and the amount of silver present as silver chloride.

In connection with the use of Protargol as a remedy, it is of great interest to state that solutions of this preparation have a good buffer value for silver ions between p_{Ag} 2.8 and 4.0, as can be read from the curves. Therefore, it is evident that the silver-ion concentration will vary but slightly, when the protargol is introduced into a liquid of the body that contains small amounts of chloride.

Summarizing the results—we stated that all the silver in Protargol can react with a halide, in which case it is transformed into the corresponding silver halide. In contradistinction to this, Collargol consists mainly of metallic silver, a small amount probably being present in the form of silver oxide; this we determined by means of a potentiometric titration with iodide in acid solution. Moreover, from the latter titration could be concluded that our preparation, Collargol, contained 5% silver as silver chloride.

BRIEF SUMMARY.

1. All the silver in Protargol can be titrated with iodide by the application of the potentiometric method. The first rise in potential occurs after transformation of the silver proteinate into silver iodide, the second after the transformation of silver chloride into silver iodide.
2. A Protargol solution has a good buffer value for silver ions between p_{Ag} from 2.8 to 4.0.
3. Collargol contains nearly all the silver in the metallic state; only a small part is present in the ionogenic form (oxide). The latter can be determined by means of a potentiometric titration with iodide; at the same time we find the silver present as silver chloride.

ABSTRACT OF DISCUSSION.

J. C. Munch: What chemical characteristic would most closely agree with the irritability of this type of compound? It is my understanding that silver-nitrate solution itself is no longer used because it is too irritant.

Dr. Koltzoff: You ask me why this can be used in medicine and why the silver nitrate cannot be used? I think that owing to the presence of the colloid in this case, most of the silver ions are adsorbed on the surface of the proteid. The silver-ion concentration is rather low and though you are working in a concentration of one, two, three or four per cent., you don't get increased ion concentration. It doesn't increase when you increase the concentration, or hardly increases, but when you have a solution of silver nitrate and you make a more concentrated solution, the silver-

ion concentration increases just the same as the concentration of the salt itself increases. Whereas, when you have the silver proteid the largest part of the silver ions are forming some chemical complex or colloidal complex with the proteids present, and so they don't irritate the tissues in the body.

H. B. Corbitt: You state that there is silver colloid there in the colloidal dispersion. In such a state I believe it could be carried to any part of the body, say, to the face, and might be deposited under the skin. Does the sunlight affect it? Do you know of any cases of argyria?

Dr. Kolthoff: When you take silver nitrate it is reduced in the body to metallic silver, and the metallic silver deposits in the cells just under the skin, but it is not sunlight which plays the rôle but only special characteristics of the cells of the skin that are doing that, because it is not only in the skin that you have metallic silver but also in other cells of the body. I am not quite sure where all these cells are because I am not a pharmacologist, only a chemist and pharmacist. The main part is deposited in the cells just under the skin.

A PHARMACOGNOSTIC AND CHEMICAL STUDY OF MA HUANG (EPHEDRA VULGARIS VAR. HELVETICA).

BY K. K. CHEN.*

I. INTRODUCTION.

In a preliminary report of experiments with Ma Huang (1) it was noted that the drug possessed actions very similar to those of adrenaline, and that these were due to an alkaloid which had been identified as Ephedrine. A more complete report of these experiments and of the results of administration of ephedrine to normal and diseased men has been published (2). It appears from the pharmacodynamic studies that ephedrine is of considerable value as a circulatory stimulant in surgical shock, as a bronchodilator in asthma, as a mydriatic, and as an apparently specific remedy in Addison's disease. Since ephedrine is effectively absorbed from the gastrointestinal tract, and since solutions of the alkaloid are very stable, it appears to be a drug of definite clinical value. Naturally the identification of the plant and alkaloid is of some importance.

II. HISTORY.

Ma Huang has been identified as *Ephedra vulgaris* var. *helvetica*, family *Gnetaceae* (3). In Chinese characters, *Ma* means "astringent" and *Huang* "yellow;" the former probably refers to taste and the latter to color after storage. It was tasted and placed by Emperor Shen Nung some 5100 years ago in the "medium class" (4). It entered many famous prescriptions, and appeared in "Pentsao Kang Mu," the Chinese Dispensatory written in 1596 A.D. (5). No scientific investigation was made until Nagai (6) isolated an alkaloid from it which he named ephedrine. Its empirical formula is $C_{10}H_{15}ON$; its chemical structure has been repeatedly studied (7) (8) (9) and is most probably phenyl-ol α -methyl β -methyl-amino β -ethane, $C_6H_5OH.CH.CH.CH_3.NHCH_3$.

III. GEOGRAPHICAL DISTRIBUTION.

The exact distribution of the plant requires an accurate survey. It has been reported that in China it is indigenous to the sea coast (3), to west Szechuan near

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