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A Study of Ephedrine with Silver Preparations*

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Ephedrine, one of the alkaloids of Ma Huang, has been known and used in medicine for centuries. The plant from which the alkaloid is obtained is *Ephedra equisetina*, Bunge and *Ephedra sinica* commonly known as Ma Huang. The active principle, ephedrine, was isolated in 1885 by Yamanashi, in an impure form. Nagai, with the assistance of Hori (1), in 1887, isolated ephedrine in the pure form.

The chemical behavior of ephedrine has been exhaustively studied, and the litera-

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ture is rich in references to derivatives and proof of chemical structure. Although the literature contains many references to ephedrine there are but a small number of discussions on the use of ephedrine with silver preparations.

The literature includes references to the preparation of many derivatives and homologues of ephedrine. Among the salts of ephedrine prepared are the hydrochloride, sulfate, oxalate, phosphate, nitrate, hydroiodide, hydrobromide, citrate, benzoate, salicylate and acetate. Quaternary ammonium derivatives have been prepared. A derivative recently reported is ephedrine camphorsulfonate.

Ephedrine hydrochloride and sulfate have commonly been dispensed by physicians in combination with silver proteinates for the bactericidal action of silver and the vasoconstrictor effect of ephedrine. The purpose of this investigation was concerned with the study of solutions of the ephedrine alkaloid and its salts with silver preparations, and with the preparation of silver salts of ephedrine.

Lanwermyer (2) reports that ephedrine hydrochloride and ephedrine sulfate are incompatible with silver salts. Chen and Kao (3) state that chlorephedrine treated with silver nitrate in the presence of nitric acid yields pseudoephedrine. Solutions of the silver protein compounds precipitate alkaloids from their solutions. Waldbott (4) advances the theory that silver protein compounds, due to their alkalinity, precipitate alkaloids.

Further work on the incompatibility of alkaloids with certain silver proteins was carried out by Pilcher (5). He concludes from his experiments that the organic silver preparations inactivate epinephrine within a few hours. Therefore, epinephrine should not be used in these combinations unless freshly prepared.

Rebiere (6) reports that very dilute solutions of silver, gold or palladium salts, when heated with epinephrine in alkaline media, are reduced with the formation of a colloidal solution, and by the addition of a protective colloid the solution can be made stable.

Numerous compounds of silver with basic substances are described in the literature, but there is no reference to ephedrine silver compounds. In most of the basic compounds silver has a coordinate valency of two (7). The silver halide or nitrate is known to combine with two molecules of ammonia, pyridine, aniline, quinoline and like compounds.

The preparation of complex silver compounds of hexamethylenetetramine with silver chloride, silver oxalate and other silver salts has been reported. Complex salts of alpha amino acids, quinine silver phosphate, ethylenediamine silver phosphate and acriflavine have all been prepared and are recommended for use in place of silver nitrate. In this investigation, several complex silver salts of ephedrine were attempted.

EXPERIMENTAL

Preparation of Silver Salts.—A number of silver salts were prepared and their reaction with ephedrine and its salts studied. Silver oleate, stearate and palmitate were prepared according to the procedure of Whitmore and Lauro (8). These salts were dry powders, insoluble in water, methyl alcohol, ether and chloroform. Oil emulsions of the silver soaps were attempted, but satisfactory preparations could not be obtained.

Complex silver salts of alpha amino acids were attempted using glycine and silver oxide (9). A stable complex salt was not obtained. The crystals produced decomposed before they could be separated from the reaction mixture and dried. The preparation of a complex salt, using silver sulfate and glycine, was attempted but failed.

Silver lactate was prepared by double decomposition of sodium lactate and silver nitrate. Grayish white, fluffy crystals, soluble in water, were obtained.

Hexamethylenetetramine silver nitrate was prepared by mixing dilute solutions of silver nitrate and hexamethylenetetramine (10). Fine, white crystals, unstable in aqueous solution, were obtained. A stable solution of hexamethylenetetramine silver nitrate was prepared using a large excess of hexamethylenetetramine.

Colloidal silver chloride was prepared by mixing a solution of silver nitrate with a sodium chloride, gelatin solution. Colloidal silver was prepared according to a method described by Schwyzer (11).

Preparation of Salts of Ephedrine.—Ephedrine stearate and oleate were obtained as liquids by neutralizing alcoholic solutions of the fatty acids with ephedrine. Ephedrine phosphate was prepared by neutralizing dilute phosphoric acid with the alkaloid. The tartrate was prepared by mixing a

Table I.—Reaction of One Per Cent Aqueous Solution of Ephedrine with Silver Salts

Per Cent Solution of Silver Salt	Results
1. Hexamethylenetetramine silver nitrate 0.5% solution	The silver salt was reduced to a silver mirror in two days
2. Hexamethylenetetramine silver nitrate 0.5% solution with no ephedrine (control)*	The solution remained clear for ten days, then a silver mirror was produced
3. Silver nitrate 5% solution	A brown precipitate was immediately produced. Upon standing the silver salt was reduced to a silver mirror
4. Silver nitrate 5% (control)	Solution remained clear
5. Hexamethylenetetramine solution	After eight days the silver salt was reduced to a silver mirror
6. Hexamethylenetetramine solution (control)	Solution remained clear
7. Silver lactate 5% solution	After three days the silver salt was reduced to a silver mirror
8. Silver lactate 5% solution (control)	Remained clear

* The control solutions contained no ephedrine.

methyl alcohol solution of ephedrine and tartaric acid and precipitating ephedrine tartrate with ether.

Reaction of Ephedrine with Silver.—In order that the reactions of ephedrine with different silver salts and preparations could be determined, a number of aqueous solutions of silver salts were added to one per cent aqueous solutions of ephedrine alkaloid. A one per cent solution of ephedrine with 5 per cent silver nitrate reduced the salt to metallic silver. Also a one per cent solution of ephedrine reduced silver sulfate in aqueous solution to metallic silver.

The action of ephedrine alkaloid was tested with the silver salts which were prepared in this work. The reaction of ephedrine with these silver salts is tabulated in Table I.

The silver soaps being insoluble in water were made into ointments containing one per cent of ephedrine alkaloid. Upon standing the ointments became very black and were characterized by a very disagreeable odor.

A series of experiments were completed using ephedrine salts with a saturated solution of silver salts and preparations to determine whether the alkaloidal salts had the reducing property of the base. One per cent aqueous solutions of ephedrine salts were mixed with a saturated solution of silver sulfate, a saturated solution of hexamethylenetetramine silver nitrate, a one per cent solution of silver lactate, and a 10 per cent solution of Neo-Silvol. In Table II will be found the results of the above experiments.

From the results of the experiments shown in Table II it is evident that the ephedrine salts do not have the reducing property of the free alkaloid.

A preparation of 5 per cent silver oleate in olive oil was made by incorporating 1.0 Gm. of ephedrine oleate thoroughly with the oil preparation. It darkened upon standing, but when compared with an oil preparation of silver oleate, free of alkaloid, they appeared to be the same. Apparently the ephedrine salt had no reducing action.

To solutions of colloidal silver chloride, one per cent ephedrine, one per cent ephedrine hydrochloride and one per cent sulfate were added. The results of these experiments are shown in Table III.

From the results obtained in the reactions of ephedrine with silver salts, the use of the free base, ephedrine, reduced the silver salts to metallic silver. However, if the basic property of ephedrine was neutralized by the formation of a salt and the salt used in solutions with silver salts there was apparently no reduction of the silver salts. Apparently, as shown in Table III, the use of ephedrine and ephedrine sulfate with colloidal silver was satisfactory.

Table II.—Effect of Ephedrine Salts in Solution of Organic Silver Preparations and Silver Sulfate

Ephedrine Solutions	Silver Solutions	Remarks	Cu-NaOH Test
a. Ephedrine sulfate 1%	Silver sulfate sat. sol.	Solutions remained clear for three days, after that time a black precipitate formed	+
Ephedrine sulfate control		Clear solution	+
	Silver sulfate control	Solution remained clear for three days	-
b. Ephedrine sulfate 1%	Hexamethylenamine AgNO ₃ sat. sol.	Solution remained clear for seven days and then changed to a slight amber color. No precipitate	+
	Control	After a few days, a slight deposit of silver	-
c. Ephedrine sulfate 1%	Silver lactate 1%	Solution remained clear for 24 hours. No sediment. A fine black precipitate was formed	+
Ephedrine lactate 1%	Silver lactate 1%	The same results obtained as the above solution	+
	Silver lactate 1% (control)	Clear solution from one to twenty-five days. Fine black sediment was produced	-
d. Ephedrine sulfate 1%	Neo-Silvol 10%	No change in appearance from that of the control	+
	Neo-Silvol 10% (control)	The colloidal particles settle out on standing but were easy to disperse in solution by shaking	-

Table III.—Reaction of Ephedrine and Ephedrine Salts with Colloidal Silver Chloride

Ephedrine Solutions	Colloidal Silver Chloride	Samples 1 and 2	Cu-NaOH Test
1. Ephedrine 1%	One ounce	No change occurred in the solution after 14 days	+
2. Ephedrine hydrochloride 1%	One ounce	White precipitate immediately produced on standing	+
3. Ephedrine sulfate 1%	One ounce	No change occurred in the solution	+
4.	One ounce (control)	Sedimentation occurs upon standing which is easily dispersed by shaking	-

Preparations of Ephedrine Silver Salts.—Various compounds of silver with basic substances are described in the literature. It is known that silver halide or nitrate combines with two moles of ammonia, pyridine, aniline and other related substances. Ephedrine, being a basic substance, should combine with silver. The combination of a salt was attempted using freshly precipitated silver chloride and ephedrine in alcoholic solution. This mixture was refluxed for three hours. The silver salt was reduced to metallic silver. The process was repeated using ephedrine hydrochloride with the same result.

A preparation of a complex salt of ephedrine silver phosphate was undertaken. This compound was prepared by dissolving freshly precipitated silver phosphate in syrupy phosphoric acid, then adding ephedrine alkaloid until the solution was saturated. A yellow crystalline mass was obtained from the acid solution. This substance was partially soluble in water leaving an insoluble yellow residue. The residue was analyzed and found to be silver phosphate. The aqueous portion was evaporated nearly to dryness and colorless needle-shaped crystals were precipitated with alcohol. These crystals were identical with ephedrine phosphate.

The results of this experiment show that the acid solution was apparently a mixture of ephedrine phosphate and silver phosphate in phosphoric acid.

A preparation of colloidal silver with ephedrine was obtained that was apparently quite stable. This colloidal solution was made by adding a solution of silver nitrate to a gelatin ephedrine solution containing a small amount of 10 per cent ammonia water. A dark brown preparation was obtained which showed no tendency to form sediment. The colloidal solution contained 0.38 per cent silver.

Silver compounds of basic substances have been prepared by using the hydrochloride of the base. An example of this is silver arspenamine dihydrochloride. An attempt was made to prepare silver ephedrine by using ephedrine hydrochloride and silver nitrate in methyl alcohol solution. This solution was refluxed for a period of three to four hours and then filtered. The filtrate obtained was evaporated to remove the methyl alcohol. A yellow crystalline residue was obtained which was soluble in water and methyl alcohol, but insoluble in ether. The crystalline residue was assayed for silver and found to contain 11 per cent silver. However, on recrystallizing the silver salt was precipitated and filtered off. The filtrate was evaporated to dryness and a compound was obtained that was free of silver. This crystalline substance was apparently

an isomer of ephedrine. A silver compound with the basic substance, ephedrine, apparently could not be prepared.

It was shown in previous experiments that ephedrine was stable with silver in an acid solution. A double salt of silver ephedrine tartrate should be stable. A combination of ephedrine silver tartrate was prepared by mixing a methyl alcohol solution of ephedrine and tartaric acid with a methyl alcohol solution of silver nitrate. This reaction mixture was refluxed for several hours. A white precipitate was first formed which was silver tartrate. This precipitate, silver tartrate, was filtered off and the filtrate evaporated over a water-bath to remove the methyl alcohol. A syrupy amber-colored material was obtained which changed to a semi-crystalline substance on cooling and was soluble in water but insoluble in methyl alcohol and ether. The semi-crystalline mixture was thoroughly washed with ether; fine, slightly yellow powder was obtained which was soluble in water. An aqueous solution of the powder gave an acid reaction to litmus, a white precipitate was formed on addition of dilute hydrochloric acid, and a purple color was produced with the copper sulfate, sodium hydroxide reaction. The melting point of the dry powder ranges from 105–144° C. which indicates a mixture of two compounds and not a true chemical compound. This compound was found by analysis to contain 10.5% silver, and to be a mixture of ephedrine nitrate and silver tartrate.

DISCUSSION

The results obtained in attempting to prepare silver compounds of ephedrine show that the basic property of ephedrine must be different from other basic organic compounds such as aniline, pyridine, quinoline and other like compounds. In the preparation of ephedrine silver chloride, metallic salt was apparently reduced to a silver oxide with no combination with the basic nitrogen of ephedrine. In the experiment preparing ephedrine silver nitrate, a mixture was obtained that upon recrystallizing from water precipitated a silver salt leaving a yellow crystalline compound free of silver. However, a colloidal solution of ephedrine and silver nitrate was prepared

and was apparently stable. The mixture of ephedrine silver tartrate obtained was apparently a stable mixture. The dry powder had not changed in appearance upon standing for one month.

CONCLUSIONS

From the information obtained in this work the following conclusions may be drawn:

1. Ephedrine alkaloid in aqueous solution reduced silver salts to metallic silver. The ephedrine salts do not have the reducing property of the alkaloidal base.

2. Ephedrine or ephedrine sulfate appeared to be stable in solution with colloidal silver chloride. A colloidal solution of ephedrine silver nitrate was prepared which was apparently stable.

3. Ephedrine phosphate and silver phosphate, in strongly acid solution, were apparently stable. No chemical compound was produced. Ephedrine phosphate and silver phosphate were isolated and identified.

4. Silver compounds with ephedrine, such as ephedrine silver chloride and ephedrine silver nitrate, could not be prepared. Ephedrine hydrochloride was apparently converted into pseudoephedrine by the reaction of silver nitrate in alcoholic solution.

5. A mixture of ephedrine and silver tartrate was obtained that was apparently stable in aqueous solution. The compound was found by analysis to contain 10.5 per cent silver and to be a mixture of ephedrine nitrate and silver tartrate.

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The Histology of *Salvia Officinalis**

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The need for a thorough and comprehensive investigation of the histology of *Salvia officinalis*, L., became apparent when it was deemed of such importance as to merit a place in the National Formulary, Sixth Edition. An investigation of the literature revealed that in most cases *Salvia* was mentioned in connection with other species of the same genus, only in broad general discussions of the characteristic features of the *Labiates*, of which family it is a member. The number of different species belonging to this family is so large that many of them, including *Salvia*, have not individually received the meticulous histological study they deserve.

The early literature contains only brief and incomplete descriptions of *Salvia officinalis* leaf and stem, but there are many references to adulterants. The recent work by Youngken and Vander Wyk (1) on a sample of *Salvia* obtained from the Harvard University Garden, Cambridge, Massachusetts, does not entirely agree with the findings made in the course of the present investigation. Hence, it is obvious that to facilitate the exclusion of adulterants and to aid in the identification of genuine *Salvia*, a study of additional material obtained from another geographical source is needed. An amplification of the histology of this drug is, therefore, sufficient justification for a work of this kind.

The present monograph on *Salvia* in the National Formulary (2) gives a brief description of the leaf powder. It admits the presence of not more than ten per cent of the

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