

DISTINCTIVE PROPERTIES AND CLASSIFICATION OF ORGANIC AND COLLOIDAL SILVER COMPOUNDS.*

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I. OBJECTS.

A large number of silver protein compounds are now on the market, and it is desirable to classify these in a logical manner. Collargol, Argyrol and Protargol, for instance, evidently represent quite distinct types. May the other compounds be arranged under these three types, or are further groups necessary? What should be the criteria for a classification? The following investigation is intended as a partial and tentative answer to these questions. It includes the application and the discussion of a series of tests and data to the silver-protein and colloidal silver compounds accepted in "New and Non-official Remedies"¹ and of a few which have not yet been accepted.²

2. TESTS AND DATA.

Condition of the Silver.—Silver ions precipitate ordinary proteins and are therefore highly irritant to the tissues. Compounds containing their silver in non-ionized or "masked" or "colloidal" form do not precipitate and therefore largely avoid the irritation. This is the main object in the therapeutic use of these silver compounds. Various precipitant reactions may be used as tests for free silver ions. The most convenient, perhaps, is the precipitation of chlorides. A modification of this will be described later.

It may be stated now that all but two of the preparations contain all of their silver in non-ionized form; and these two (Albargin and Roche Silver Nucleinate) contain only a small, but not negligible, amount of ionized silver, presumably as a contamination.

Total Silver Content.—The quantities claimed by the manufacturers are shown in Table I. It will be noted that the content of the three typical compounds, collargol, argyrol and protargol, are distinctive; and the most of the other compounds approach one or the other of these types. It remains to be seen whether this coincides with other distinctive properties. Actually this is very generally the case.

Protein Component.—This is not very important, since it is practically a mere vehicle. Some of the manufacturers prefer to keep its nature secret, as a valuable manufacturing asset. Others follow the much more reprehensible course of giving misleading names to their proteins. This abuse is not easily stopped, since there is no known method for identifying the protein in the finished product. The data, as far as known, are shown in Table I.

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¹ Electrorgol was not included, because of its very low silver content.

² Silver proteinate, Heyden; Silver nucleinate and proteinate, Roche; Solargentum, Squibb; and Silvol.

TABLE I.—TOTAL SILVER CONTENT, AND PROTEIN COMPONENT.

Drugs (arranged in order of silver content).	Claimed percentage of silver.	Claimed protein base.
Collargol.....	78	
Cargentos.....	50	
Argyrol.....	20-25	Vitellin (in reality probably denatured egg albumen)
Squibb Silver Prot.....	19-23	Gelatin
Roche Silver Nucl.....	20	Probably denatured serum albumen
Solargentum.....	about 20	Gelatin
Silvol.....	20	?
Sophol.....	20	Methylen nuclemic acid
Albargan.....	15	Gelatin
Novargan.....	10	Albumin(?)
Protargol.....	8.3	Albumin(?)
Heyden Silv. Prot.....	8.3	Albumin(?)
Roche Silv. Prot.....	8.0	(?)
Hegonon.....	7	Albumose
Argonin.....	4.28	Casein

Antiseptic Efficiency.—The silver-protein compounds are used almost exclusively on mucous membranes, for antiseptic or astringent, or for demulcent effects. A classification according to antiseptic efficiency would be desirable, but does not appear feasible at present. The results of culture experiments cannot be transferred with confidence to clinical conditions; and no satisfactory technic has been developed for life-tests.

Irritation.—This is perhaps the most important criterion for a clinical classification. It is easily judged by placing a few drops of the 1 : 10 watery solutions¹ in the nostrils, and in case of doubt also in the conjunctival sac. The method is subjective and incapable of absolute quantitative expression. Nevertheless the differences are sufficiently striking to permit arrangement into three groups, as in Table II.

The data refer to a 1:10 aqueous solution in the nostrils. Those which were also tried in the conjunctiva are marked **.

TABLE II.—IRRITATION.

No irritation.	Slight but distinct.	Marked irritation.
Argyrol.....	Protargol	
Argonin (5%).....	Heyden Silv. Prot.	
Silvol**.....	Cargentos	Albargin ²
Sophol.....	Silv. Nucl. Roche	
Squibb Sil. Prot.....	Silv. Prot. Roche** (very slight ²)	
Novargan.....	Hegonon** (very slight)	
Collargol.....		
Collargol Old (5%)....		
Solargentum.....		

Albumen Precipitation.—This is in a sense an index of astringency. However, it was observed that some non-irritant preparations may, nevertheless, give a

¹ 1 : 10 Solution of the Silver Salts: 0.5 Gm. of the salt is dissolved in 5 Cc. of distilled water. This solution is also used for the egg-test, the absorption test, and the color index.

² Albargin gives a precipitate with sodium chloride. The filtrate from this appears less irritant. This suggests that the irritation is due largely, if not solely, to free silver ions.

precipitate with albumen. This is most conspicuous with silver. It may be that, in this case, the precipitation is due to a change of the colloidal state of the silver compound rather than in the albumen.

However, the test as elaborated, at least helps to distinguish certain of the compounds that are otherwise closely related. It is also an objective confirmation of the distinct though slight astringent action of all the members of the protargol type (Protargol, Roche and Heyden Silver Proteinate; and Hegenon); and of the marked astringent action of those containing free silver ions (Albargin; Roche Silver Nucleinate).

Technic of the Egg Test.—About $\frac{1}{2}$ inch (about 2 Cc.) of undiluted egg white is placed in a test-tube. To this is added 1 Cc. of 1 : 10 solution of the silver salt. They are thoroughly mixed by shaking, then allowed to stand for about 15 minutes, and then diluted with 15 Cc. of water. If this is too deeply colored, more water may be added. (The egg-white must be added undiluted, as stated.) The results are shown in Table III.

TABLE III.—ALBUMEN PRECIPITATION.

<i>The mixture remains clear:</i>	<i>The mixture is distinctly turbid:</i>
Argyrol	Protargol
Squibb's Silver Prot.	Novargan
Solargentum Squibb	<i>There is a distinct precipitation:</i>
Collargol	Heyden Silver Prot. (curdy)
<i>The mixture is nearly clear:</i>	Cargentos (very fine)
Argonin	Silvol (very fine)
Sophol	Silv. Nuclein Roche (curdy)
Silv. Prot. Roche	<i>Abundant curdy precipitate:</i>
Hegenon	Albargin (2 samples)
	<i>Unsuited for test</i>
	Collargol, old sample

Adsorption.—The difference between the preparations are presumably based largely upon differences in their colloidal state. It was attempted to demonstrate them by the behavior toward adsorbents. "Permutit" was found to have no distinct effect on argyrol solutions and very little on protargol. "Lloyd's reagent," however, showed characteristic differences in the decolorization for the members of each group, although it had no apparent relation to a broader classification.

Technic.—One Cc. of a 1 : 10 solution of the silver salt is diluted with 0.5 Gm. of "Lloyd's Reagent" (Hydrated Aluminum Silicate), allowed to stand for a few minutes, and filtered. The color of the filtrate is noted.

The degree of decolorization is shown in Table IV.

TABLE IV.—ADSORPTION OF COLOR BY "LLOYD'S REAGENT."

Practically completely destroyed.	Considerably destroyed.*	Little, if any, decolorized.
Argyrol	Protargol	Cargentos
Albargin (2 samples)	Silv. Prot. Heyden	Collargol
Argonin	Novargan	Sophol
Collargol, old sample	Silvol	Solargentum Squibb
Silv. Nuclein Roche	Hegenon	Silver Prot. Squibb
Silv. Prot. Roche		

* These are arranged in order of decreasing adsorption, the protargol filtrate being the least colored, and hegenon the most.

To a portion of the filtrate (further diluted if too dark) is added a drop of 25% sodium chloride, to reveal free silver ions. (Silver nitrate, even in very dilute solution, is not adsorbed by Lloyd's Reagent.)

Free Silver Ions.—The sodium chloride test is conveniently applied to the filtrate from the Lloyd's Reagent. The test was found negative with all but Albargin (two samples) and with the sample of Roche's silver nucleinate.

The presence of free silver ions renders the solutions irritant, and therefore defeats the special object of the protein compound.

Solubility Behavior.—Table V shows that nearly all the protein silver compounds dissolve promptly and completely, at least to 25%, when placed in contact with water. The most conspicuous exception is Argonin, which dissolves slowly and imperfectly, like dried serum.

A strikingly abnormal solution behavior is also shown by an old sample of Collargol, which could not be suspended in water. This had been kept in an amber, glass-stoppered bottle probably for over ten years.

TABLE V.—SOLUBILITY BEHAVIOR.

The following observations were recorded in making the 25% solutions:

Solution complete and very prompt:

Argyrol

Solution complete and prompt:

Protargol

Roche's Silv. Nucleinate

Squibb's Silv. Prot.

Silvol

Solution complete and fairly prompt:

Albargin

Hegonon

Heyden Silv. Prot.

Novargan

Sophol

Solargentum

Solution fairly prompt, but not quite complete:

Roche Silv. Prot.

Undissolved, sticky mass, 10% also incomplete, 1% is turbid:

Argonin

Permanent colloidal solution when triturated in water:

Cargentos

Collargol

Not miscible with water:

Collargol, old sample

Specific Gravity of 25 Percent Solutions.—Some ophthalmologists use the protein-silver compounds, especially the Argyrol type, for their specific gravity rather than for their antiseptic effect, the idea being that the heavier silver solutions would displace the secretions, pus and bacteria by gravity. Some such mechanical action would doubtless occur, if the patient is placed in the proper position; but if this has any value it would be obtained equally well, and much more cheaply, by a 25% solution of acacia.

The "25%" solutions were made by dissolving 0.5 Gm. of the substance in 1.5 Cc. of distilled water. The specific gravity was determined by weighing 1 Cc.

in an Ostwald pipette, at 20° C. The results are shown in Table VI, in descending order.

TABLE VI.—SPECIFIC GRAVITY OF 25% SOLUTIONS.

Collargol.....	1.230
Cargentos.....	1.166
Solargentum.....	1.159
Argyrol.....	1.147
Acacia.....	1.137
Silvol.....	1.137
Sophol.....	1.132
Roche Sil. Nucl.....	1.123
Albargin.....	1.112
Heyden Silv. Prot.....	1.108
Protargol.....	1.104
Roche Silv. Prot.....	1.100
Hegonon.....	1.093
Novargan.....	1.090
Squibb Silv. Prot.....	1.088

Argonin is not soluble to 25%. A 2.5% solution has the specific gravity—1.010.

Viscosity of 25 Percent Solutions.—This has no special relation to the natural groups, and is probably without clinical significance. It was estimated by the time of outflow from a 1 Cc. Ostwald pipette (from the 1 Cc. mark, to the junction of bulb and beak), at 20° C. The results shown in Table VII are arranged in descending order.

TABLE VII.—VISCOSITY OF 25% SOLUTIONS.

Name.	Seconds required for outflow. (Water = 40 seconds.)	Viscosity. (Water = 1.)
Hegonon.....	285	7.125
Sophol.....	180	4.125
Albargin.....	174	4.350
Squibb Silv. Prot.....	135	3.375
Cargentos.....	120	3.0
Roche Sil. Nucl.....	102	2.550
Protargol.....	75	1.875
Novargan.....	71	1.775
Argyrol.....	54	1.350
Heyden Silv. Prot.....	53	1.325
Silvol.....	50	1.250

Acacia: The 25% solution flowed too slow for measurement. A 10% solution (1 Gm. + 9 Cc.) flowed in 165 seconds, corresponding to a viscosity of 4.125.

Argonin, Collargol, Solargentum, and Roche's Silv. Prot. did not dissolve completely, and thus could not be measured.

APPEARANCE OF THE COMMERCIAL PRODUCTS: This is only of incidental interest. The specimens may be arranged as follows:

Coarsely granular

- Argyrol (dull black masses)
- Collargol, old sample (dull gray-black masses)
- Collargol, fresh sample (brilliant steel blue granules)
- Solargentum (bright black granules)

Bright black scales:

Cargentos
 Silv. Nucl. Roche
 Silv. Prot. Squibb
 Silvol

Coarse Powders:

Albargin (appearance of dried albumen)
 Argonin (buff)

Fine powders: (arranged in order of decreasing depth of color)

Heyden Silv. Prot. (dark red to dark chocolate tint)¹
 Sophol (chocolate)
 Protargol (reddish brown)¹
 Roche Silv. Prot. (milk chocolate)
 Hegonon (milk chocolate)
 Novargan (buff)

Depth and Color of Transparency of 1 : 1000 Solutions.—This is a rough but useful aid to identification. The clearness or turbidity to reflected light appears related to the natural groups, the colloidal silver and the protargol type being generally turbid, whereas the argyrol type is generally clear.

For making the comparisons, one Cc. of 1 : 10 solution is added to 100 Cc. of water in a conical "urine-glass." The results are shown in Table VIII.

TABLE VIII.—APPEARANCE OF 1 : 10000 SOLUTIONS.

	Solution clear both with transmittent and reflected light.	Clear with transmitted light, but turbid by reflected light.	Turbid but with transmitted and reflected light.
Color very deep.....		Cargentos	Collargol
Color deep.....	Argyrol Silvol Solargentum Silv. Prot. Squibb	Silv. Nucl. Roche	
Color moderate.....	Hegonon Protargol ² Silv. Prot. Heyden Silv. Prot. Roche	Albargin Sophol	
Partially colored.....	Novargan		

Argonin has a different, violet tinge, and is turbid both by transmitted and reflected light.

Color Index.—Colorimetric measurements furnish a more accurate quantitative expression of the color-intensity. This is fairly characteristic for the groups, the collargol group standing the highest, the argyrol group intermediate, and the protargol group lowest. There are, however, individual exceptions. The color intensity increases with the silver content, but not in simple proportion.

Technic.—The 1 : 1000 to 1 : 50,000 solutions are compared with tenth normal potassium dichromate in a Duboscq colorimeter, set at 20. The tints do not match well, but sufficiently so to express the great difference in intensity.

The *simple color index* expresses the ratio of the color intensity of the 1 : 1000 solution of the silver compound, to the tenth-normal dichromate solution.

The *silver color index* is the simple index, divided by the percentage of silver in the compound. The results are shown in Table IX, with the compounds arranged in descending order of silver-color index.

¹ Different samples of Protargol and Heyden's Silver proteinate vary considerably in color.

² Different samples of Heyden's Silver Proteinate and of Protargol vary materially in color.

TABLE IX.—COLOR INDEX.

Name of substance.	Dilution.	Match of tint.	Reading.	Simple index.	Silver index.
Collargol.....	50,000	fair	16	62.5	0.80
Heyden Silv. Prot. (average).....	3.14	0.39
Cargentos.....	10,000	good	12	16.7	0.33
Silvol.....	10,000	good	31	6.5	0.30
Roche Silv. Nucl.....	10,000	fair	34	6.0	0.30
Argyrol.....	10,000	fair	48	4.2	0.20
Squibb Silv. Prot.....	10,000	good	47	4.3	0.20
Protargol (average).....	0.80	0.10
Roche Silv. Prot.....	1,000	fair	28	0.72	0.09
Hegonon.....	1,000	poor	50	0.4	0.06
Sophol.....	1,000	poor	40	0.50	0.025
Albargin.....	1,000	very poor	55	0.36	0.024

3. CLASSIFICATION OF THE PROTEIN AND COLLOIDAL SILVER COMPOUNDS.

The study of the preceding data has led to the compilation of the properties most useful for grouping. These are shown in Table X.

TABLE X.—CLASSIFICATION AND SIGNIFICANT PROPERTIES OF PROTEIN AND COLLOIDAL SILVER COMPOUNDS

Principal types. Members.	"Collargol." Collargol. Cargentos.	"Argyrol." Argyrol. Squibb Silv. Prot. Sophol. Silvol. Solargentum(?)	"Protargol." Protargol. Roche Silv. Prot. Heyden " Hegonon.	"Free Silver." Albargin. Roche Silv. Nucl.	"Pale" Norvagan Argonin.
Sliver content.....	50 to 78	20 to 25	7 to 8.5	*	4 to 10
Irritation.....	*	None	Slight but distinct	Marked	*
Albumen precipitation....	*	*	More or less	Positive	*
Adsorption of color.....	None	*	More or less	*	*
Free silver.....	None	None	None	Present	None
Spec. Grav. of 25% sol... Transparency of 1 : 1000 sol. by reflected light..	1.160 to 1.230 * *	1.132 to 1.147 Clear (except Sophol)	1.093 to 1.108 Clear	* * Turbid	* * *
Simple color index.....	16.7 to 62.50	4.2 to 6.5 (ex- cept Sophol, 0.50)	0.37 to 1.75	*	Very low
Silver color index.....	0.33 to 0.80	0.20 to 0.30 (ex- cept Sophol, 0.025)	0.044 to 0.20	*	Very low

4. DISTINCTIVE CHARACTERS OF THE INDIVIDUAL DRUGS.

These are arranged by groups and shown in Tables XI to XIV.

* = Inconstant or not characteristic.

TABLE XI.—DISTINCTIVE CHARACTERS OF THE ARGYROL TYPE.

Members.	Argyrol.	Squibb's Silv. Prot.	Sophol.	Silvol.	Solargentum.
Silver percent (claimed).....	20-25%	19-23	20	20	About 20
Irritation by 10% sol.....	None	None	None	None	None
Albumen.....	No precipitate	No prec.	Nearly clear	Distinct prec.	No precipitate
Lloyd's reagent, filtrate.....	Complete decolorization	Not decolorized	Not decolorized	Consid. decolorization	Deeply colored
Free silver (chloride test).....	None	None	None	None	Absent
Solution.....	Very prompt	Prompt	Fairly prompt	Prompt	Permanent
Sp. Gr. of 25%... 1.147		1.088	1.132	1.137	1.159
Viscosity of 25%... 1.350		3.375	4.5	1.250	
Appearance.....	Dull black mass	Bright black scales	Fine chocolate powder	Bright black scales	Brilliant black granules
Color of 1:1000 sol.	Deep	Deep	Moderate	Deep	Deep
Transparency by reflected light....	Clear	Clear	Turbid	Clear	Clear by both transmitted and reflected light
Sample color index.	4.2	4.3	0.50	6.5	
Silver color index...	0.20	0.20	0.025	0.30	5.0
Nature of Protein base.....	Denatured albumen	Gelatin	Methylen nucleinate acid	?	0.25

TABLE XII.—DISTINCTIVE CHARACTERS OF THE COLLOIDAL SILVER TYPE.

Members.	Cargentos.	Collargol (recent sample).
Percent silver (claimed).....	50	78
Irritation by 10% sol.....	Slight, but distinct	None
Albumen.....	Fine precipitate	No precipitate
Lloyd's reagent, filtrate.....	Deeply colored	Deeply colored
Free silver (chloride test).....	Absent	Absent
Solution.....	Permanent	Permanent
Spec. Grav. of 25%.....	1.166	1.230
Viscosity of 25%.....	3.0	
Appearance.....	Bright black scales	Brilliant steel blue granules
Color of 1 : 1000 sol.....	Very deep	Very deep
Transparency.....	Clear by transmitted light, turbid by reflected	Turbid, both with transmitted and reflected
Simple color index.....	16.7	62.5
Silver color index.....	0.33	0.80

TABLE XIII.—DISTINCTIVE CHARACTERS OF THE PROTARGOL TYPE.

Members.	Protargol.	Roche Silv. Prot.	Heyden Silv. Prot.	Hegonon.
Silver percent (claimed).....	8.3	8.0	8.3	7.0
Irritation by 10% sol.....	Distinct	Very slight	Distinct	Very slight
Albumen.....	Turbid	Nearly clear	Almost clear to curdy precipitate	Nearly clear
Lloyd's reagent, filtrate.....	Considerably de-colored	Completely de-colored	Considerably de-colored	Some what de-colored
Free silver (chloride test).....	None	None	None	None
Solution.....	Prompt	Limited	Fairly prompt	Fairly prompt
Sp. Gr. of 25% sol.	1.104	1.100	1.108	1.093
Viscosity of 25% sol.....	1.875		1.325	7.125
Appearance.....	Reddish brown, fine powder	Fine, milk chocolate powder	Fine, red to dark chocolate powder	Fine, milk chocolate powder
Color of 1 : 1000 sol.	Moderate	Moderate	Moderate to deep	Moderate
Transparency by reflected light....	Clear	Clear	Clear to turbid	Clear
Simplex color index	Av., 0.80 (0.37, 0.72 0.77, 1.25)		Av., 3.14 (0.96, 0.4 1.75, 6.7)	
Silver color index..	Av., 0.10 (0.044, 0.09 0.09, 0.15)		Av., 0.39 (0.12, 0.06 0.20, 0.80)	
Nature of protein base.....	?	?	?	Albumose

TABLE XIV.—DISTINCTIVE CHARACTERS OF SUNDRY TYPES.

Members.	Atypical. Novargan.	Atypical. Argonin	Free silver ions. Albargin.	Free silver ions. Roche Silv. Nucleinate.
Silver percent (claimed).....	10.0	4.28	15.0	About 20
Irritation by 10% sol.....	None	None (5%)	Marked	Distinct
Albumen.....	Turtid	Nearly clear	Abundant curdy precipitate	Curdy precip- itate
Lloyd's reagent, filtrate.....	Considerably de- colorized	Completely de- colorized	Completely de- colorized	Completely de- colorized
Free silver (chloride test).....	None	None	Present	Present
Solution.....	Fairly prompt	Limited & gummy	Fairly prompt	Prompt
Sp. Gr. of 25% sol..	1.090		1.112	1.123
Viscosity of 25% sol.....	1.775		4.35	2.55
Appearance.....	Fine, buff powder	Coarse, buff powder	Coarse powder like dried albumen	Bright, black scales
Color of 1:1000 sol.	Pale	Pale	Moderate	Deep
Transparency by reflected light....	Clear	Turbid	Turbid	Turbid
Simple color index.			0.36	6.0
Silver color index..			0.024	0.30
Nature of protein base.....		Casein	Gelatin	?

SUMMARY.

The colloidal and silver compounds may be arranged into a few typical groups:

The Collargol Group, comprising Collargol and Cargentos.

The Argyrol Group, Argyrol, Squibb's Silver Proteinate, Sophol, and Silvol and Solargentum.

The Protargol Group: Protargol, Roche's Silver Proteinate, Heyden Silver Proteinate, and Hregon.

The Free Silver Group: Albargin and Roche's Silver Nucleinate.

The Pale Group: Novargan and Argonin.

The distinctive data of these groups are shown in Table X; the detailed data are reproduced in Tables I to IX, arranged according to the tests; and in Tables XI to XIV, arranged according to the drugs.

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