

observation, the first two require a dose 72% larger. That this is not accidental is shown by the fact that the figures are so clear cut and have appeared earlier in different relationships. Absorption, however, slow as it is, is complete by the fourth hour and is fairly uniform for different tinctures, as is shown by the individual figures. It would seem that this feature of slow absorption from the lymph sac of the frog as shown by these tinctures is another example of the same difficulty which is exhibited by the strophanthus preparations when they are given by mouth to the higher animals.

The digitalis tinctures differ considerably from the strophanthus tinctures in details of absorption (Table III), although they require, as is to be expected, a larger dose by both lymph sac methods than by the intravenous route. Absorption, however, is apparently as complete in one hour as in four, as the ratio of dosage is the same for four hours as it is for one hour. These results are in interesting contrast to those obtained with strophanthus and they emphasize the relative ease of digitalis absorption as compared with strophanthus. It must be remembered that only three tinctures are being considered and these relations might be altered were a larger number of digitalis powders examined. This criticism or warning is offset somewhat by the fact to which attention was called earlier, *viz.*, that these assays were carried out very carefully by two different workers in two different years and in the rare cases when slightly discordant results were obtained which could not be reconciled by repeated assays, an average of the results was taken. We feel, therefore, that the figures and conclusions drawn therefrom are entitled to considerable respect.

CONCLUSIONS.

The powdered digitalis which is proposed as an International standard is about 30% stronger than the U. S. P. X standard.

With the strophanthins and with the tinctures of strophanthus, a dose 10% larger is necessary to cause systolic standstill of the frog's heart in four hours when it is given into the lymph sac than when the drug is given intravenously and one hour allowed for observation.

A dose of the strophanthins 40-50% larger is required in the 1-hour lymph sac method than in the 1-hour intravenous method.

For tinctures of strophanthus the dose when it is given into the lymph sac and one hour allowed for observation, must be almost double the intravenous dose.

For tinctures of digitalis, the dose, whether for a 1-hour or for a 4-hour period of observation, must be about 65% above the intravenous dose, indicating greater ease of absorption of digitalis from the lymph sac as compared with strophanthus, as absorption is practically complete in one hour.

ORGANIC ADDITION COMPOUNDS OF CALCIUM CHLORIDE AND CALCIUM IODIDE.*

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It is a well-established fact, that calcium chloride forms a number of addition compounds with organic substances. Thus ethyl alcohol and methyl alcohol

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form addition compounds with calcium chloride in which the water of crystallization of calcium chloride is replaced by ethyl or methyl alcohol. For this reason calcium chloride cannot be used to dehydrate ethyl alcohol.

Another addition compound of calcium chloride is catechol calcium chloride of the following composition: $\text{CaCl}_2 \cdot 3\text{C}_6\text{H}_4(\text{OH})_2$ described by F. R. Weinland and Wilhelm Denzel (1) and triglycerin calcium chloride of the formula: $\text{CaCl}_2 \cdot 3\text{C}_3\text{H}_5(\text{OH})_3$ described by A. Grün and T. Husman (2).

Another addition compound described in the literature is calcium chloride thiourea, $\text{CaCl}_2(\text{CS}(\text{NH}_2)_2)_6$, which was studied by A. Rosenheim and V. J. Meyer (5). Calcium chloride tetraacetamide, and calcium chloride dihydrazine are also described in the literature (3) (4).

The calcium chloride urea was the first of these addition compounds to find therapeutic application. This compound of the composition of $\text{CaCl}_2 \cdot 4\text{CO}(\text{NH}_2)_2$ is patented (6) and marketed under the name of "Afenil." "Afenil" is used wherever calcium chloride is indicated; its toxic properties being less than that of calcium chloride.

According to the patent, calcium-chloride urea is prepared by dissolving urea in ethyl or methyl alcohol and dissolving calcium chloride in the solvent. These solutions are then poured together and the ethyl or methyl alcohol evaporated until crystallization takes place.

During this investigation, a number of calcium chloride addition compounds were prepared for therapeutic use with the thought of detoxicating calcium chloride. The method described in the "Afenil" patent was used. Compounds similar to urea were selected until finally it was observed that calcium chloride combines with most of the basic substances, that have the same solubility properties. It was also noticed that each organic compound in combination with calcium chloride, also reacted with calcium iodide. Calcium iodide, therefore, was also included in this investigation. A point of interest noted was, that calcium chloride combines with two or four molecules of the organic substance, while calcium iodide usually combines with six molecules. The following addition compounds of CaCl_2 and CaI_2 were prepared:

Calcium chloride thiourea: $\text{CaCl}_2 \cdot 4\text{CS}(\text{NH}_2)_2$

Calcium chloride hexamethylenetetramine, $\text{CaCl}_2 \cdot 2\text{C}_6\text{H}_{12}\text{N}_4 \cdot 3\text{H}_2\text{O}$

Calcium chloride thiosinamine, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CS} \\ \diagup \text{NH}_2 \\ \diagdown \text{NH}-\text{CH}_2-\text{CH}=\text{CH}_2 \end{array}$

Calcium chloride urethane, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CO} \\ \diagup \text{NH}_2 \\ \diagdown \text{O}-\text{C}_2\text{H}_5 \end{array} \cdot 2\text{H}_2\text{O}$

Calcium chloride antipyrine, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CH}_3 \\ \diagup \text{C} \\ \diagdown \text{N} \\ \text{CH}=\text{CO} \\ \diagup \text{N} \\ \diagdown \text{N} \end{array}$

Calcium chloride acetylurea, acetylafenil, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CO} \\ \diagup \text{NH}_2 \\ \diagdown \text{NHCOCH}_3 \end{array}$

Calcium chloride acetylthiourea, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CS} \\ \diagup \text{NH}_2 \\ \diagdown \text{NHCOCH}_3 \end{array}$

Calcium chloride monophenylurea, $\text{CaCl}_2 \cdot 4 \begin{array}{l} \text{CO} \\ \diagup \text{NH}_2 \\ \diagdown \text{NHC}_6\text{H}_5 \end{array}$

From the calcium iodide compounds the following were prepared:

Calcium iodo urea, manufactured in Germany and also called "Iodofortan" (8) of the following formulas: $\text{CaI}_2 \cdot 6\text{CS}(\text{NH}_2)_2$

Calcium iodo thiourea, prepared in analogy to "Iodofortan," $\text{CaI}_2 \cdot 6\text{CS}(\text{NH}_2)_2$

Calcium iodo hexamethylenetetramine, $\text{CaI}_2 \cdot 2\text{C}_6\text{H}_{12}\text{N}_4$

Calcium iodothiosinamin, $\text{CaI}_2 \cdot 4\text{CO}$ $\begin{array}{l} \diagup \text{NH}_2 \\ \text{NH}-\text{CH}_2-\text{CH}=\text{CH}_2 \\ \diagdown \end{array}$

Calcium iodo urethane, $\text{CaI}_2 \cdot 6\text{CO}$ $\begin{array}{l} \diagup \text{NH}_2 \\ \diagdown \text{OC}_2\text{H}_5 \end{array}$

Calcium iodo antipyrène, $\text{CaI}_2 \cdot 6\text{CH}_3-\text{C}$ $\begin{array}{l} \diagup \text{N} \begin{array}{l} \text{CH}_3 \\ \text{C}_6\text{H}_5 \end{array} \\ \diagdown \text{N} \\ \text{CH}-\text{CO} \end{array}$

Calcium iodo monoacetylurea, $\text{CaI}_2 \cdot 6\text{CO}$ $\begin{array}{l} \diagup \text{NH}_2 \\ \diagdown \text{NHCOCH}_3 \end{array}$

Calcium iodomonoacetylthiourea, $\text{CaI}_2 \cdot 6\text{CS}$ $\begin{array}{l} \diagup \text{NH}_2 \\ \diagdown \text{NHCOCH}_3 \end{array}$

and Calcium iodomonophenylurea, $\text{CaI}_2 \cdot 6\text{CO}$ $\begin{array}{l} \diagup \text{NH}_2 \\ \diagdown \text{NHC}_6\text{H}_5 \end{array}$

EXPERIMENTAL PART.

"Afenil," calcium chloride urea was prepared according to the German Patent previously mentioned (6).

From Aqueous Solution.—12 Gm. of urea were dissolved in 20 cc. of water and 5.5 Gm. of anhydrous calcium chloride dissolved in 20 cc. of water. These two solutions were mixed and heated to the boiling for about half an hour, then boiled until the volume was very small. On cooling white crystals, rhombic prisms were obtained.

From Methyl Alcoholic Solution.—12 Gm. of urea dissolved in 50 cc. of hot methyl alcohol and 5.5 Gm. of anhydrous calcium chloride dissolved in 150 cc. of hot methyl alcohol, the two solutions mixed and then the alcohol was distilled off until the compound began to crystallize. The addition of ether will cause precipitation. A white somewhat hygroscopic powder was obtained, with a melting point of 158–160° C. Analysis for calcium chloride urea gave for calcium 11.3%, 11.7% calculated for calcium 11.4%. It is easily soluble in water and in dilute alcohol; insoluble in absolute or 96% alcohol.

Calcium Chloride Thiourea.—15 Gm. of thiourea were dissolved in hot methyl alcohol and 5.5 Gm. of calcium chloride were dissolved in hot methyl alcohol; the two solutions mixed and the alcohol removed to a very small volume and then precipitated with ether. It is a white crystalline, homogeneous substance, monocline prisms, melting point 175–177° C. very readily soluble in water and alcohol, insoluble in ether. Slightly soluble in acetone. Analysis gave

Calcium calculated:	9.7 %
Calcium found:	8.5 %
Nitrogen calculated:	27.05%
Nitrogen found:	27.60%

Although the compound was described in the literature (5) the calcium chloride thiourea obtained in this investigation was different in composition from the one previously described by A. Rosenheim and V. Meyer.

Calcium Chloride Hexamethylenetetramine.—This compound was described in the literature (7) and was prepared accordingly, resulting in white crystals, very soluble in water, soluble in absolute alcohol, insoluble in ether and acetone. Analysis for

Nitrogen calculated: 25.7 %
Nitrogen found: 25.78%

Calcium Chloride Thiosinamine.—In the preparation 23 Gm. of thiosinamine and 55 Gm. of anhydrous calcium chloride were dissolved in hot methyl alcohol. The methyl alcohol was removed by heating on a water-bath, the remaining fluid crystallized in the cold. A white crystalline powder was obtained, very soluble in water and methyl alcohol, insoluble in absolute ethyl alcohol and acetone. Melts at 75° C.

Analysis: Nitrogen calculated: 17.8 %
Nitrogen found: 17.3 %

Calcium Chloride Urethane.—This was prepared for the first time in the same way as all the other compounds. White crystals soluble in water, insoluble in acetone and ether, soluble in alcohol.

Analysis: Nitrogen calculated: 21.8 %
Nitrogen found: 22.3 %
Calcium calculated: 4.6 %
Calcium found: 4.5 %

Calcium Chloride Acetylurea, Acetylafenil.—Prepared for the first time from 20.4 Gm. of acetyl urea and 5.5 Gm. of calcium chloride, resulting in white crystals melting at 135–140° C. Slightly soluble in cold water, soluble in hot water, hot methyl and ethyl alcohol, insoluble in ether.

Analysis: Nitrogen calculated: 21.8 %
Nitrogen found: 22.3 %
Calcium calculated: 7.7 %
Calcium found: 7.8 %

Calcium Chloride Acetylthiourea.—5.5 Gm. of anhydrous calcium chloride and 23.2 Gm. of monoacetylthiourea were dissolved in hot methylalcohol, the methyl alcohol removed by distillation until crystallization takes place.

Analysis: Nitrogen calculated: 19.24%
Nitrogen found: 20.03%, 18.55%, 18.26%

It represented a white, somewhat hygroscopic powder, soluble in cold and hot water, soluble in methyl alcohol and ethyl alcohol, insoluble in ether.

Finally from the calcium chloride series, calcium chloride monophenyl urea was prepared as follows:

2.75 Gm. of anhydrous calcium chloride was dissolved in hot methyl alcohol and 13.6 Gm. of monophenyl urea in hot methyl alcohol; the alcohol was removed by distillation until crystallization took place. A white crystalline substance, which was insoluble in cold water, soluble in boiling water, soluble in methyl and ethyl alcohol and in soluble in ether, was obtained.

The analysis gave: Nitrogen calculated: 15.4 %
Nitrogen found: 15.2 %
Calcium calculated: 5.5 %
Not determined: —

From the calcium iodide the following addition compounds were prepared

Calcium Iodo Urea.—This compound is manufactured in Germany (8) under the name of "Iodofortan" by the Chemische Fabrik Arthur Jaffe, Berlin and was prepared from 7.3 Gm. of calcium iodide and 9 Gm. urea. It yielded a white, slightly hygroscopic substance, melting point 95° C. and is very soluble in cold and hot water, methyl alcohol and ethyl alcohol.

Nitrogen calculated:	25.7 %
Nitrogen found:	26.2 %
Calcium calculated:	6.1 %
Calcium found:	7.5 %

The compound absorbed moisture, which accounts for the poor analytical results. In analogy with calcium iodourea, calcium iodo thiourea was prepared for the first time.

Calcium Iodo Thiourea.—This was prepared from 7.35 Gm. of calcium iodide 11.4 Gm. of thiourea.

Analysis:	Nitrogen calculated:	22.4 %
	Nitrogen found:	21.5 %
	Calcium calculated:	5.3 %
	Calcium found:	4.3 %

It is a white and stable substance, very soluble in water, in methyl and ethyl alcohol, containing about 34% of iodine. Its elimination in regard to iodine was studied by F. R. Greenbaum and G. W. Raiziss (9).

Calcium Iodo Hexamethyleneamine.—This is manufactured in Germany under the name of "Hexamine," prepared from 7.35 Gm. of calcium iodide and 7 Gm. of hexamethyleneamine. It gave a nice white stable substance, not hygroscopic readily soluble in water and in hot methyl alcohol, insoluble in absolute alcohol, acetone and ether. Melting point 180°C.

Analysis:	Nitrogen calculated:	19.5 %
	Nitrogen found:	18.4 %
	Calcium calculated:	6.9 %
	Calcium found:	5.3 %

The compound was apparently still moist or had absorbed moisture when analyzed.

Calcium Iodo Thiosinamine.—This is prepared from 7.3 Gm. of calcium iodide and 24 Gm. of thiosinamine, dissolved in methyl alcohol and evaporated to dryness. It is fluid at 90° C. but crystallizes on cooling. White crystals, soluble in water, insoluble in alcohol, ether and acetone.

Analysis:	Nitrogen calculated:	16.8 %
	Nitrogen found:	17.2 %
	Calcium calculated:	4.0 %
	Calcium found:	4.5 %

Calcium Iodo Urethane.—Obtained from calcium iodide and urethane. 13.35 Gm. of urethane and 7.3 Gm. of calcium iodide were dissolved in methyl alcohol and the methyl alcohol was distilled off. Yellow crystals, stable on air, soluble in water and methyl alcohol, insoluble in absolute alcohol and ether.

Analysis:	Nitrogen calculated:	10.1 %
	Nitrogen found:	9.4 %
	Calcium calculated:	4.8 %
	Calcium found:	4.5 %

Calcium Iodo Antipyrone.—Prepared from 7.35 Gm. of calcium iodide and 21.2 Gm. of anti-pyrone; it yielded white crystals, soluble in water and methyl alcohol, insoluble in ether.

Analysis:	Nitrogen calculated:	11.3 %
	Nitrogen found:	10.18%, 10.2%
	Calcium calculated:	2.7 %
	Calcium found:	2.9 %

Calcium Iodo Monoacetyl Thiourea.—4.5 Gm. of monoacetyl thiourea and 1.8 Gm. of calcium iodide were dissolved in hot methyl alcohol and then the alcohol evaporated. White powder slightly soluble in cold water, soluble in hot water, soluble in ethyl and methyl alcohol, insoluble in ether.

Analysis:	Nitrogen calculated:	16.7 %
	Nitrogen found:	15.5 %
	Calcium calculated:	3.9 %
	Calcium found:	2.4 %

Calcium Iodo Acetyl Urea was prepared from 14.7 Gm. of calcium iodide and 30.6 Gm. of acetyl urea. Slightly soluble in cold water, more soluble in warm water, soluble in ethyl and methyl alcohol, insoluble in ether.

Analysis:	Nitrogen calculated for nitrogen:	18.6 %
	Nitrogen found:	18.9 %

Calcium Iodo Monophenyl Urea was prepared from 17 Gm. of monophenylurea and 6.2 Gm. of calcium iodide, dissolved in methyl alcohol and the alcohol was removed by distillation and ether added.

Analysis:	Nitrogen calculated:	15.13%
	Nitrogen found:	15.89%

It represents a white crystalline substance, insoluble in cold water and soluble in hot and boiling water, in methyl alcohol and ethyl alcohol and insoluble in ether.

It was attempted to use phenyl-acetyl-urea of the formula: $\begin{array}{l} \diagup \text{NHCOCH}_3 \\ \text{CO} \\ \diagdown \text{NHC}_6\text{H}_5 \end{array}$, and

it was found that this compound does not form an addition product with either calcium chloride or calcium iodide.

CONCLUSIONS.

1. Calcium chloride and calcium iodide form addition products with organic compounds of a pronounced basic nature, whereby in the case of calcium chloride usually four molecules of the organic base enter into the addition combination; in the case of calcium iodide six molecules of the organic compound enter into this combination.

2. Calcium chloride and calcium iodide form addition compounds with urea and thiourea derivatives, as long as both amino groups or at least one of the amino group is not substituted.

3. These addition compounds are stable, less hygroscopic than calcium chloride and calcium iodide, with a definite crystalline shape and are only formed, when the calcium chloride as well as the organic compounds are easily soluble in the same solvents.

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