preparation. It is, therefore, hoped that the deoleated tincture of strophanthus will be made an official preparation to replace the tincture of the U. S. P. VIII.

In the estimation of the author, tincture of strophanthus is to be preferred to the tincture of digitalis, which is generally supposed to undergo rapid deterioration. This belief, however, was strongly disputed by Hatcher & Eggleston[2], but there are many facts yet to be established before such a radical view can be accepted.

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ON CRYSTALLINE KOMBE'-STROPHANTHIN.

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(Continued from page 618.)

Properties of strophanthidin. Under the magnifying glass strophanthidin shows the same shape of crystals as shown in the picture of strophanthidin given by Feist. It contains one molecule of water of crystallization. Feist had trouble in drying the substance and it was only by obtaining crystals of a methyl alcohol containing strophanthidin, which gave off readily the methyl alcohol at 100° C. that he could establish the formula for dry strophanthidin. Feist, and also Heffter and Sachs, did not dry in a heated vacuum, but only at ordinary pressure. By drying in vacuo at 110-115°, we could readily obtain crystalline water-free strophanthidin. Also at lower temperature (105° in vacuo) the water is given off, but slowly. In moist air the water is taken up again. Found: 3.56%, 3.50% and 3.02% calculated for $C_{27}H_{38}O_7 + H_2O$: 3.66% H_2O.

Melting point. Strophanthidin melts at about 120°C in its water of crystallization to a turbid mass and melts at about 170°C. The dried substance melts as Feist describes at 169°-170°C, foaming at 180°C, it becomes solid by cooling and then melts at 232°.

Specific rotation. 1.008 gm. air dry strophanthidin (from crystalline strophanthin) was dissolved in 25 cc. methyl alcohol.

$$(\alpha)_D = \frac{100\alpha}{lc} = +44.26 \qquad l = 2 \qquad \alpha = +3.57°$$

0.3300 gm. air dry strophanthidin (from amorph. acid strophanthin) was dissolved in 25 cc. methylalcohol.

$$(\alpha)_D = \frac{100\alpha}{lc} = +44.26 \qquad l = 2 \qquad \alpha = +1.17°$$

Feist found for 0.5043 gm. strophanthidin dissolved in 25 cc. methyl alcohol

$$(\alpha)_D = +45.45$$

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[2] Paper read before April meeting New York Branch of A. Ph. A.

Combustion.

I. 0.2196 gm. air dry strophanthidin (from cryst. strophanthin) gave 0.1598 gm. H_2O and 0.5300 gm. CO_2.

A second combustion was made of air dry strophanthidin (from cryst. strophanthin trade) which was not purified by recrystallization from alcohol, but was used as it is obtained in splitting the crystalline strophanthin according to Kohn and Kulisch.

After having been thoroughly washed with water it was dried in air.

II. 0.2198 gm. air dry strophanthidin (not recrystallized) gave 0.1660 gm. H_2O and 0.5312 gm. CO_2.

or in percent:

	I	II	Calc. f. $C_{23}H_{32}O_7+H_2O$
C	65.82	65.91	65.80
H	8.16	8.46	8.20

Thus it is apparent that recrystallization does not alter the constitution.

III. 0.2054 gm. strophanthidin (from cryst. strophanthin) dried at 110-115° in vacuo gave 0.1499 gm. H_2O and 0.5164 gm. CO_2.

IV. 0.2330 gm. strophanthidin (from amorph. acid strophanthin) dried at 110-115° in vacuo gave 0.1770 gm. H_2O and 0.5845 gm. CO_2; or in percent:

	III	IV	Calc. f. $C_{23}H_{32}O_7$
C	68.57	68.41	68.30
H	8.18	8.01	8.09

Quantitative estimation of strophanthidin in crystalline strophanthin.

0.5000 gm. air dry crystalline Kombe strophanthin was placed in a 200 cc. Erlenmeyer flask with 25 cc. 1% H_2SO_4 and boiled one hour with a reflux condenser. The separated strophanthidin was caught on a quantitative filter. The filtrate and wash water (about 50 cc.) was distilled to 25 cc. and boiling continued with a reflux for one-half hour. The separated strophanthidin was caught on the same filter paper and this process once more repeated. The total yield of strophanthidin was dried in vacuo, giving 0.2638 gm., or 52.76%.

0.500 gm. of air dry crystalline Kombe strophanthin was placed in a 200 cc. Erlenmeyer flask with 22 cc. of 2.2% HCl (twice the volume of the same strength HCl as used by Kohn and Kulisch) and boiled one-fourth hour with a reflux condenser, cooled and filtered; the filtrate concentrated to original volume and boiling continued with reflux condenser for one-fourth hour. After cooling, the separated strophanthidin was caught on the same filter and dried in vacuo, giving 0.2533 gm., or 50.46%.

Quantitative estimation of strophanthidin in amorphous Kombe strophanthin.

0.500 gm. air dry amorphous Kombe strophanthin Merck was placed in an Erlenmeyer with 50 cc. 0.5% HCl and heated to 75° and further treated, according to the method of Feist, repeating the heating three times. Dried in a vacuo, 0.2218 gm. strophanthidin was obtained, or 44.36%.

0.5000 gm. air dry amorphous Kombe strophanthin Merck was placed in an Erlenmeyer with 25 cc. of 1% H_2SO_4 and treated as the first determination on crystalline Kombe strophanthin. This gave 0.2234 gm. of vacuum dry strophanthidin, or 44.78%.

The largest yield of strophanthidin obtained by Heffter and Sachs from crys-

talline Kombe strophanthin (air dry) was 58%, from amorphous Kombe strophanthin 50%, and from hispidus strophanthin 45%.

Air dry crystalline Kombe-strophanthin $C_{40}H_{56}O_{15} + 3\,H_2O$ contains 57.11% anhydrous strophanthidin ($C_{27}H_{38}O_7$).

It is interesting to note that the yield of strophanthidin from amorphous Kombe strophanthin and from hispidus strophanthin is less than from crystalline Kombe-strophanthin, thus indicating (cf. the later pentose estimation in amorphous strophanthin) that the non-strophanthidin moiety is larger in hispidus and amorphous Kombe-strophanthin than in the crystalline Kombe strophanthin.

CRYSTALLINE KOMBE-STROPHANTHIN.
Table of Comparisons.

Strophanthin.	Fraser	Arnaud	Kohn & Kulisch. a)	Feist. b)	Heffter & Sachs.	Own investigations.	
						By spontan. crystal of alcoh. extr.	
How prepared.	Ppt. by tannic acid and dec. by PbO.	Removed impur. by basic lead.	Same as Arnaud.	Same as Fraser.	About same as Arnaud.	Cry. stroph.	Am. acid stroph.
Reaction with H_2SO_4	green	.....	red	green	dark green	dark green	red-green
Melting point of dried str.	173°	165° not dried	179°	170°	177-181°	178-179°	180°
Average % of hydr. water.	.....	.....	.....	7.48	.....	6.3	6.9
Spec. Rot. of watery sol..	.....	+30	inact. or neg.	+10.12	+28.72	+28.7	+20.6
How dried for comb.	.....	110°	105-109°	100-105°	105-110°	105-110°	105-110°
Aver. % C....	55.43	60.54	60.57	56.17	61.93	61.97	60.50
Aver. % H....	7.56	8.00	7.71	7.36	7.64	7.98	7.62
Aver. % OCH_3	.....	.....	3.58	3.64	4.73	.....	.....
Mol. wgt.....	.....	.....	.....	679	.....	783	.....
Strophanthidin %	.....	.....	52.5	50-52	56-58	50-53	.....
Strophanthidin prep. by action of	.....	.....	boil 2.4% HCl	0.5% HCl at 75°	0.5% HCl at 75°	boil 4% and 1% HCl	boil 1% H_2SO_4
Melt p. of dried	.....	.....	193°	169-170° foam 176°	169-173° foam 178°	170° foam 180°	170-180°
Aver. % hydr. water	.....	.....	.....	7.0	.....	3.6	3.3
Spec. Rot. alcoh. sol....	.....	.....	.....	+45.45	+41.49	+44.26	+44.3
How dried f. comb.....	.....	.....	in vac. + H_2SO_4	c)	vac. + H_2SO_4	vac. at 110°	vac. at 110°
Aver. % C....	.....	.....	71.07	68.32	66.44	68.57	68.41
Aver. % H....	.....	.....	8.63	8.02	8.07	8.18	8.01
Aver. % OCH_3	.....	.....	5.6	No OCH_3	No OCH_3	.....	.....
Mo. wgt.....	.....	.....	.....	474	.....	.....	.....
Rhamnose estim.	.....	.....	.....	1 mol. rham	.....	none	none
OCH_3 in sugar	.....	.....	.....	6.25	.....	.....	.....

(a) Strophanthin prepared by Merck from hispidus gave Kohn and Kulisch the same results.
(b) Strophanthin prepared by Schuchardt from hispidus gave Feist the same result.
(c) Strophanthidin containing chrystalmethylalcohol was dried at 100°.

From this table, it seems very probable that Arnaud separated the same crystalline strophanthin as we did, but by recrystallizing it, converted it into the amorphous one and using amorphous strophanthin for his combustion (supposing it to be a hydrate, which by drying could give off the water) came to wrong conclusions.

The strophanthin of Kohn and Kulisch has a different specific rotation and gives by splitting a different strophanthidin, which may be due to the method of cleavage.

It would be interesting to investigate other strophanthus species, or to prepare Kombe-strophanthin from Strophanthus Kombe seed at different stages of ripe-

ness in an endeavor to obtain the strophanthin of Kohn and Kulisch. It may be stated here that the formula and cleavage equation which Feist[25] deduced from the data of Kohn and Kulisch best interpret their results.

The table shows the exact coincidence of our results with the analytical data of Heffter and Sachs; with the exception of the figures for the combustion of strophanthidin and the quantitative estimation of strophanthidin.

Heffter and Sachs seemed to have the same difficulty as Feist in obtaining an anhydrous strophanthidin. It is interesting to note that drying in a heated vacuum readily yields an anhydrous strophanthidin. This is shown by the agreement of the analytical data with the calculated figures and with the data obtained by Feist for his strophanthidin, which was obtained by driving off methyl alcohol from methyl alcohol containing strophanthidin.

The quantitative estimation of strophanthidin, applied by Heffter and Sachs, gives undoubtedly the best results.

When we compare the results of Feist with our own, the question arises: Are the differences due to the use of Fraser's method? By applying the method of Fraser on Strophanthus Kombe seed a difficulty arises, how to remove the lead and the nitrogen. The same trouble was mentioned by Thoms[26], who presented another method which gave him an ash and nitrogen free amorphous strophanthin. Gerrard[27] also stated that the method of Fraser is not clearly published and suggests the removal of the lead with hydrogen sulphide. When we compare the first and second methods of preparation used by Fraser (mentioned before) we observe, that in the one first described the lead is removed by passing carbon dioxide for *several hours* through the solution of strophanthin; in the second method, carbon dioxide is passed for *two or three days*. It would seem, therefore, that Fraser himself had trouble in removing the lead. The explanation of this is that there is present a lead salt of acid strophanthin which cannot be decomposed by CO_2. Boehringer & Sons, who prepared the strophanthin used by Feist in his experiments, followed the process of Fraser. By applying the method of Gerrard (which is similar to Fraser's) a brittle amorphous ash and nitrogen-free strophanthin was obtained which contained 7.04% H_2O (dried at 105° in vac.) 0.2983 gm. strophanthin (acc. to Gerrard) dried at 105° in vacuo gave 0.1938 gm. H_2O and 0.5945 gm. CO_2, or in percent:

C=58.82 and H=7.80.

Although the investigations are not yet finished, it can be stated that at least two closely related glucosides are present. One, the crystalline Kombe-strophanthin, and another apparently amorphous strophanthin, both yielding the same strophanthidin. The acid amorphous strophanthin obtained from the crystalline glucoside, while showing nearly the same molecular weight, is found, as will appear later, to be only one-third as toxic to frogs as the crystalline strophanthin. The strophanthin investigated by Fraser and by Feist is probably identical with the amorphous preparations of strophanthin prepared by Heffter and Sachs (the analytical data are not taken up in the table) and with the preparation which

[25] Berichte, 1900, 33, p. 2067.
[26] Berichte, 31, p. 271 and 404.
[27] Pharm. Jour. and Trans., 17 (1887), p. 923.

we made according to the method of Gerrard. The toxicity of this amorphous preparation is almost the same as that of crystalline strophanthin. If this amorphous strophanthin were merely a mixture of crystalline strophanthin, and its acid amorphous modification, this mixture would be less toxic than that of the crystalline variety unless it contained, besides the two, another of greater toxicity than that of the crystalline strophanthin. As no such product is known, it follows that only a minute quantity of the acid derivative is associated with the naturally occurring amorphous strophanthin.

Rhamnose is an easily crystallizable substance and readily yields methylfurfurol. It is thus difficult to understand why Feist was unable to obtain rhamnose in a crystalline state, notwithstanding that he obtained strophantobiose methylether as a crystalline body, and only by distilling this sugar complex with 30% sulphuric acid was methylfurfurol indicated. It is perhaps not superfluous to consider the close relationship of l-mannose and rhamnose as seen by the structural formula (Winther[28] and Hudson[29]).

We found further that in large amounts mannose does yield a furfurol derivative. Five gm. d-mannose gave 0.269 gm. blackish brown phloroglucid. According to Alberda van Ekenstein and Blanksma[30] no furfurol, but β-oxy δ-methylfurfurol is formed by the action of hydrochloric acid on hexoses. Both are precipitated by phloroglucine. Amorphous Kombe strophanthin Merck was also distilled with 12.5% HCl in an endeavor to obtain the phloroglucid of (methyl) furfurol. 1.000 gm. of amorphous strophanthin Merck yielded 0.0568 gm. of a dark green phloroglucid, which indicated a pentose. According to the formula of Tollens (Journ. f. Landwirtschaft 1900, p. 379):

$$\text{pentose} = (A + 0.0052) \times 1.017$$

gives 6.3% pentose.

Another experiment 1.000 gm. amorphous strophanthin Merck yielded 0.0577 gm. dark green phloroglucid, or 6.4% pentose.

We have not as yet determined whether this phloroglucid is a mixture of methyl and furforol phloroglucid.

Two molecules of crystalline Strophanthin united by a pentose can explain these observations, but further experiment must decide.

[28]Berichte, 28, p. 3000.
[29]Jour. of Americ. Chem. Soc., 1910, 32, p. 345, and p. 889.
[30]Chemisch Weekblad, 1909, p. 217.

APPENDIX.

While it is known that more than 20 different species of Strophanthus seed may be present on the market[31] there are but three different strophanthins (Kombe-strophanthin, hispidus-strophanthin and gratus-strophanthin or ouabain) of which any chemistry is known. It is a little astonishing that only at the end of a controversy of very well known pharmacognosists and botanists, regarding the question, "What kind of Strophanthus for the Pharmacopoeia, in relation to the question, what kind of Strophanthus should be taken for culture," Arthur Meyer[32] comes to the conclusion that it would be better to investigate first:

1. Which glycosides are contained in the seed of Strophanthus Kombe and of Strophanthus hispidus? Are they the same or different?

2. Is the clinical action of both drugs and the respective glycosides the same? If not, which drug is to be preferred?

In this paper we have attempted to answer the question relative to the chemistry of Strophanthus Kombe, and Heffter and Sachs have done like service for the Strophanthus hispidus seed.

In connection with the results of Heffter and Sachs the following experiments, which have been made with unidentified Strophanthus hispidus seed, seem to us also worthy of publication. We were able to obtain on the N. Y. market 17 kg. of Strophanthus hispidus seed which could be used for experiment.

3.5 kg. powdered hispidus seeds were extracted twice with petroleum ether and gave 950 gm. of a green oil, or 27.1%.

The remaining fat-free powder was percolated with eight times its weight of 70% alcohol. The alcohol was distilled off in vacuo until about 1 liter fluid remained. This fluid was purified with lead subacetate solution and further treated as described before, but no crystals of a glucosid could be obtained. Therefore, we tried to prepare the strophanthidin out of this extract. A large amount of strong alcohol was added, the precipitate filtered and the alcohol of the filtrate removed by distillation in vacuo.

The following method was used: 30 gm. of the thick extract was boiled with 150 cc. 1 % H_2SO_4 in an Erlenmeyer flask of 500 cc. capacity, until the fluid becomes just turbid. The fluid is now quickly cooled to about 50° and the oily brown drops are broken with a glass rod against the walls of the Erlenmeyer flask, until all is reduced to a yellowish white crystalline powder. It is important to do this exactly, though it takes about one-half hour to get it powdered in this way. The strophanthidin can be sucked off on a hardened filter and washed with a little warm water until neutral. The yield of impure strophanthidin was about 10 gm. This strophanthidin was repeatedly recrystallized from boiling alcohol.

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[31] Blondel. Journ. de Pharm. et de Chem., 1888, I, p. 297.
[32] Gilg: Berichte der Deutsch. pharm. Gesellsch., 1902, p. 183.
Arthur Meyer: Archiv. d. Pharm., 245, p. 351.
Hartwich: Apoth. Zeit. 22, p. 1017.
Gilg: Bericht. der deutsch. pharm. Gesellsch., 18, p. 284.
Arthur Meyer: Archiv. d. Pharm., 246, p. 541.

After separating the impure strophanthidin the filtrate, when again boiled for 20 minutes and treated in the same way, gave but a small yield of strophanthidin.

Properties. Under the microscope this purified strophanthidin shows the same shape of crystals as Kombe strophanthidin.

Melting point. The air dried and anhydrous strophanthidin has the same melting point as Kombe strophanthidin. At about 130°C the air dried substance softens and at 170° C. it melts. The fused mass resulting from melting and cooling the air dried product now melts at about 235° C. By drying in vacuo at 110° C.-115° C., strophanthidin free from water of crystallization could be obtained. Found: 2.9% H_2O calculated for $C_{27}H_{38}O_7 + H_2O$, 3.66% H_2O.

Specific rotation. 0.5900 gm. air dry strophanthidin was dissolved in 25 cc. methyl alcohol.

$l = 2$ $\qquad$ $(\alpha)D = \frac{100\alpha}{lc} = 44.07$

$\alpha = +2.08$

Found for Kombe strophanthidin $(\alpha)D = +44.29$.

Combustion.

I. 0.2345 gm. air dry strophanthidin gave 0.1721 gm. H_2O and 0.5681 gm. CO_2.

II. 0.2076 gm. air dry strophanthidin gave 0.1489 gm. H_2O and 0.5027 gm. CO_2.

Or in percent

	I	II	Calculated for $C_{27}H_{38}O_7+H_2O$
C	66.06	66.04	65.80
H	8.22	8.04	8.20

III. 0.2339 gm. strophanthidin dried at 110°-115° in vacuo gave 0.1654 gm. H_2O and 0.5848 gm. CO_2.

Or in percent:

	III	Calculated for $C_{27}H_{38}O_7$
C	68.17	68.30
H	7.93	8.09

From the conformity of these physical and chemical properties we conclude that this strophanthidin and Kombe strophanthidin are identical.

It was not possible to obtain a crystalline glucosid out of these strophanthus hispidus seeds, but the strophanthidin obtained from this glucosid could be identified.

It seems important for a systematic study of the strophanthus seed species and for related species in general to differentiate between their strophanthidins. A quantitative estimation of the strophanthidin not only forms a convenient method for chemical assays, but also their identification is an important factor in determining the species.

PHYSIOLOGICAL.

The physiological activity of crystalline Kombe strophanthin was investigated by the method of Houghton[33] for the standardization of heart tonics of the digitalis series.

This method is based on the minimum lethal dose to frogs. As there is considerable variation in the lethal dose of this series for frogs at different seasons, etc., it becomes necessary, in order to obtain comparable results, to determine, not the toxicity of the sample per se, but its ratio to that of a heart tonic prepa-

[33] Jr. Am. Med. Ass., Vol. 31, p. 959, 1895.

ration of definite strength (the standard). We are thus independent of variation in the resistance of frogs. The minimum lethal dose of the standard is an *experimental* value, while the heart tonic unit (H. T. U.)[34] is an *adopted* one and will be discussed later in connection with the experiments.

Since Kombe Strophanthus seed is adopted as official by the Pharmacopoeias of most countries, it is of real importance that the active principle of Kombe seed be used in comparing the activity of galenical preparations of strophanthus.

In the case of digitalis where a number of differently acting bodies may be present, no one can be used as a basis for comparing the therapeutic value of its galenical preparations. Therefore, since it is impossible at the present time to determine the amount of each of the active bodies, it is better to take a typical heart tonic like crystalline Kombe strophanthin for such comparisons.[35]

In the following experiments frogs (Rana Pipiens) of from ten to thirty grams were used, but with only five grams difference in the weight of frogs for any one comparison. The material was used in such concentration that about 0.5 cc. was needed for an injection. The injections were made by inserting the needle through the mouth into the ventral lymph sac. The frogs were kept in cages in a trough of running water, and at the end of twelve hours the frogs were examined and the results noted.

The toxicity of crystalline Kombe strophanthin is compared with that of some other strophanthins in Table I. The results are calculated for crystalline Kombe strophanthin, at the minimum lethal dose (M. L. D.) of 0.000001 gm. per gm. of frog, which was found to be the mean M. L. D. for the year.

TABLE I.

	M. L. D. per gm. of frogs.
Crystalline Kombe strophanthin (fr. Ident. K.)	0.000001 gm.
Amorphous acid strophanthin (derived fr. above)	0.0000031 gm.
Crystalline gratus strophanthin (Ouabain Merck)	0.00000042 gm.
Amorphous Kombe strophanthin (Merck)	0.00000094 gm.
Amorphous Kombe strophanthin (P. D. & Co.)	0.00000097 gm.
Crystalline Kombe strophanthin (fr. Kombe of trade)	0.00000095 gm.
Amorphous acid strophanthin (derived fr. above)	0.0000031 gm.

It is seen that the crystalline gratus strophanthin (Ouabain Merck) is about twice as toxic as crystalline Kombe strophanthin and the amorphous acid strophanthin from cry. K. strophanthin is practically one-third as toxic. The amorphous Kombe strophanthin, both P. D. & Co. and Merck, and also the crystalline Kombe strophanthin from trade Kombe seed, show practically the same toxicity as the crystalline Kombe strophanthin from identified Kombe seed.

The mean lethal dose was determined for crystalline Kombe strophanthin

[34] Lancet, June 19, 1909, Am. Jr. Pharmacy, Oct., 1909.

[35] It has been suggested that crystalline gratus strophanthin be used for such a standard. However, there are a number of disadvantages in its adoption.

It has never been exactly determined whether the resistance of frogs to the lethal dose of different heart tonics varies differently as the susceptibility of the frog changes with the season, etc. If crystalline Kombe strophanthin is taken as a standard this does not enter into consideration with Strophanthus preparations. With Digitalis we have a large volume of data which shows that this ratio remains very constant, while with gratus Strophanthin very little data is available which bears upon this point.

Gratus Strophanthin or Ouabain, while a nicely crystalline body may contain variable amounts of water of crystallization, and as it does not yield a crystalline strophanthidin the study of its chemistry is under a disadvantage and the identity of the glucoside is to that extent uncertain. Now that we have a crystalline Kombe strophanthin of definite physical and chemical properties that yields in addition a readily crystallizing strophanthidin so that the identity of the glucoside can be reliably determined, there is an advantage in adopting crystalline Kombe strophanthin for such a standard.

from the average of a large number of tests in comparison with a tincture of Strophanthus, of which the yearly mean lethal dose was known.

The results are found in Table II:

TABLE II.

Date.	Standard Average Tr. of Kombe Strophanthus. (1) Dose per gm. of frog in cc.	Result L.	Result D.	Crystalline Kombe strophanthin, C. P. in solution 70% alc. (2) Dose per gm. of frog in gm.	Result L.	Result D.	Corrected for Tr. killing at .000075.
1910							
Mar.	.000060	6	0				
10 to	.000065	5	4	.0000008	3	0	.00000085
22	.000070*	2	10	.0000009*	0	3	.00000097*
Apr.	.000080	5	1	.0000010	4	0	.00000088
8 to	.000085*	1	3	.0000011	1	2	.00000099
11	.000090	0	4	.0000012*	0	3	.00000106*
June	.000065	1	0	.0000008	3	1	.00000086
27, 28	.000070*	0	2	.0000009	4	1	.00000097
	.000075	0	2	.0000010*	0	6	.00000107*
July	.000060	2	0	.0000007	1	0	.0000008
23, 25	.000065*	0	3	.0000008	1	1	.00000092
	.000070	0	4	.0000009*	0	3	.00000104*
Aug. 1	.000050	5	1	.0000007	5	1	.00000088
to 3	.000055	3	4	.0000008*	1	5	.000001*
	.000060*	1	3	.0000009	0	2	.0000011
Sept.	.000055	2	0	.0000006	1	0	.00000075
6 to	.000060*	1	5	.0000007	3	1	.00000088
19	.000065	0	4	.0000008*	0	2	.0000010*
Oct.	.000070	10	0	.0000009	7	1	.0000009
28, 29	.000075*	3	7	.00000095	5	8	.00000095
				.0000010*	0	10	.0000010*
Nov. 1	.000066	2	0	.0000009	3	0	.00000094
	.000069	1	1	.00000095*	0	4	.00000099*
	.000072*	0	2	.0000010	0	3	.00000104
Dec.	.000070	2	0	.0000009	2	0	.00000084
	.000075	2	0	.0000010	3	1	.00000094
	.000080*	0	2	.0000011*	0	2	.00000103*
1911				(3)			
Mar.	.000080	4	0	.0000010	7	1	.00000084
	.000085	3	1	.0000011	4	2	.00000092
	.000090*	0	2	.0000012*	0	6	.0000010*
				(4)			
Oct.	.000055	6	2	.00000070	2	0	.00000080
28 to	.000060	4	3	.00000075	5	2	.00000086
Nov. 2	.000065*	2	10	.00000080	1	5	.00000092
	.000070	2	5	.00000085*	0	4	.00000098*
	.000075	0	5	.00000090	2	4	.00000104
				.00000095	1	8	.0000011
1912				(4)			
Apr. 25	.00006	2	0	.0000007	11	4	.00000075
May 8	.00007*	0	2	.0000008	4	8	.00000086
				.0000009*	1	7	.00000097*
				.000001	0	5	.00000107
				(5)			
July	.000055	9	2	.00000075	7	0	.00000080
24	.000060	8	8	.00000080	16	1	.00000086
Aug. 3	.000065	5	11	.00000085	7	12	.00000090
	.000070*	0	15	.00000080*	0	16	.00000097*
Average	.000072			.00000096			.00000100

(1) The standard tincture was kept in the refrigerator.

(2) The crystalline Kombe strophanthin (1 in 1000) in 70% ethyl alcohol was kept at room conditions in amber vials sealed to prevent evaporation. A solution made June 27, 1910, was used in all tests except those made April and June, 1910, unless noted.

(3) Part of these were from solution freshly made up.

(4) These were from solutions freshly made up.

(5) Part of these were from solution freshly made up, and part from solution made up September, 1911, and part from solution of June, 1910 (cf. table of permanency.)

The value .000001 gm. per gm. of frog for the M. L. D. is the mean of the first year's lethal doses for crystalline Kombe strophanthin. If the lethal dose of the standard tincture is taken at .000075 cc. per gm. of frog for the mean M. L. D. of the year, the toxicity of crystalline Kombe strophanthin comes out almost exactly .0000010 gm. per gm. of frog.

The value .000075 cc. for the average lethal dose for this tincture of Kombe Strophanthus is based on the average of a very large number of tests, extending over a number of years. It was the standard previously used for determining the strength of all the heart tonics manufactured by Parke, Davis & Co.

It seems established that the mean M. L. D. for crystalline Kombe strophanthin is .0000010 gm. per gm. of frog (Rana Pipiens of 10 to 30 gm.)

Other methods for determining the physiologic value of heart tonics were compared on this crystalline Kombe strophanthin.

The time necessary for a frog's heart to cease beating has been proposed by Focke[86] as a method for comparing heart tonic preparations.

He endeavors to determine the value of a preparation by the relation $V = \frac{P}{D.T.}$ where P is the weight of the frog, D is the dose of the material, and T is the time elapsing before complete cessation of the ventricle beat occurs.

(To be continued)

PHYTOCHEMICAL NOTES.

EDWARD KREMERS, MADISON, WIS.

Introduction.

It is almost twenty-five years ago that the writer was initiated into the realms of chemical research by his teacher and friend, Dr. Frederick B. Power, who was the first professor of pharmacy at the University of Wisconsin and who has contributed so much to plant chemical research, especially during the past ten years as director of the Wellcome Research Laboratory in London. This first experience acquainted the writer at the same time with the charm that is associated with the application of chemistry to the study of plant life, a charm that has never deserted him, though at times the pressure of other investigations and manifold duties compelled him to abandon phytochemical problems. That he has ever recurred to these problems becomes apparent, however, from the accompanying list of published notes, many of which are but fragmentary accounts.

The object of this compilation of titles is not so much to effect an inventory as it is to place in the hands of student investigators of this laboratory a con-

[86] Arch. d. Pharm. Bd. 241, p. 128. Ibid. Bd. 248, p. 345-76.