gave this treasure to his new country in exchange for liberty and independence that he found here. The devotion to his work, his strong vigor in doing the right thing at the right time, the love for art and science, these were the treasures that he brought with him from Germany and distributed here freely. During the many years of his activity, this virility, this energy and endurance, was the most remarkable trait of his individuality. He seemed never to be tired. He could work for twenty-four hours a day and still be as cheerful and vigorous as when he began, and this power of endurance stayed with him. When in his eightieth year, he took a trip to the Orient in company with a great many others, it was Ramsperger who in Egypt, in Syria, in Palestine, was always at the head of the procession. He took all the little side trips that others only half as old would not undertake for fear of fatigue, and not satisfied with this, he would occasionally sit down and write long reports on his journey which, having been collected afterwards by his son, formed a wonderful narrative of this trip.

Thus Gustav Ludwig Ramsperger will remain in our memory as a noble representative of our profession, every inch a man, without boasting, without advertising, always cheerful, always willing to work, steadfast and true to his better self, respected and beloved by all who knew him.

WILLIAM C. ALPERS.

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## COMMERCIAL CALCIUM GLYCEROPHOSPHATE.

W. A PUCKNER AND L. E. WARREN.

Glycerophosphoric acid and several of its salts were prepared by Pelouze[1] as early as 1845 while studying the constitution of glycerol. He produced the acid by heating glycerol with phosphoric acid and also with phosphoric anhydride. From the acid the barium and the calcium salts were prepared and the formula $2CaO.C_6H_7O_5PO_5$ (old atomic weights) assigned to the latter. Pelouze reported that the calcium salt was less soluble in hot water than in cold. Soon after the synthesis of glycerophosphoric acid by Pelouze, it was obtained by Gobley[2] from egg lecithin by decomposing this substance with acids. Subsequently Liebrich[3] discovered it in diseased brain tissue and in later time it has been found in a variety of animal tissues and excretions.

In 1876 Thudichum and Kingzett[4] prepared several salts of glycerophosphoric acid from the acid obtained from the brain. They prepared the anhydrous calcium salt, ignited it and weighed the calcium pyrophosphate formed. From the results of these and of elementary analyses of the salt they assigned to it the formula, $CaC_3H_7O_6P$. They also prepared an acid calcium salt from the same source, the formula of which they believed to be $CaC_3H_7O_6P.H_2C_3H_7O_3P$. In addition to the calcium salt they prepared the barium and lead salts but could not obtain

[1] Compt. rend., 21, 718 (1845).
[2] J. pharm. chim. [3], 9, 161 (1846).
[3] Annal. Chem. Pharm., 134, 29 (1865).
[4] J. Chem. Soc., 30, 20 (1876).

the copper or the silver compound in a state sufficiently stable for analysis. The barium compound was remarkable in that, if prepared by precipitation from alcohol, it was found to be a hydrated alcoholate.

In 1894 Portes and Prunier[5] described a process for preparing calcium glycerophosphate. These chemists first prepared the acid by heating 3 kg. of 60 per cent phosphoric acid with 3.6 kg. of glycerol at 110° C. for six days with occasional agitation. After cooling the mixture was saturated with calcium carbonate, the solution filtered and the calcium glycerophosphate in the filtrate precipitated by the addition of alcohol, in which solvent the salt is insoluble. The precipitate was dried in the air, dissolved in water, the solution filtered and the filtrate cautiously evaporated to dryness. The salt prepared by this process is described as a white, somewhat crystalline powder, containing 2 molecules of water of hydration. It is soluble in 15 parts of cold water but nearly insoluble in boiling water and in alcohol.

In 1894 Petit and Polonovsky[6] examined a number of the salts of glycerophosphoric acid. They reported that the calcium salt is a white powder which is soluble in 30 parts of water at 20° C. Other properties of the calcium salt were described, some of which are given herewith:

> On heating a saturated, aqueous solution of the salt a portion of the dissolved substance is precipitated in the form of scales. The aqueous solution of the salt has an alkaline reaction and is precipitated by the soluble oxalates, phosphates and carbonates and by the soluble salts of lead. The aqueous solution is not precipitated by magnesia mixture, by solution of ammonium molybdate in the cold, nor by solution of uranium acetate. If dried at 130° C. the loss should not exceed 3 per cent. If the salt be ignited the residue of calcium pyrophosphate should amount to from 55.5 per cent. to 56.5 per cent.

According to the formula given by these chemists the salt contains 1 molecule of water of hydration.

In 1897 Adrian and Trillat[7] examined seven commercial specimens of calcium glycerophosphate. They found that the product as sold at that time varied much in physical and chemical properties. According to their analyses the several specimens contained calcium equivalent to between 19.5 and 24.5 per cent of calcium oxide (13.9 and 17.5 per cent of calcium), and phosphorous equivalent to between 26 and 33 per cent of phosphorous pentoxide (11.3 and 14.4 per cent phosphorous). Of six specimens two were neutral to litmus, one alkaline and three acid. The solubility in water varied greatly, ranging from 7.6 parts of salt in 100 parts of water for the acid specimens to 4.05 parts of salt in 100 parts of water for the neutral specimens. The portion soluble in alcohol, which consisted of glycerin and phosphoric acid, ranged from 1.8 to 4.2 per cent. These chemists prepared the salt in a state of great purity by a method which differed somewhat from that employed by Pelouze. When first prepared the salt is crystalline but it rapidly loses this property when exposed to the air. The pure salt is soluble in about 22 parts of water at 25° C. Analyses indicated the formula $CaC_3H_7O_6P$. They[8] devised a method for the estimation of neutral glycerophosphates by titration with normal sulphuric acid, using methyl orange as indicator.

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[5] J. pharm. chim. [5], 29, 393 (1894).
[6] J. pharm. chim. [5], 30, 193 (1894).
[7] J. pharm. chim. [6], 6, 433 and 481 (1897).
[8] Ibid. [6], 7, 163 and 225 (1898).

Astruc[9] devised a volumetric method for the determination of the soluble glycerophosphates. He first neutralized the solution with a mineral acid, using methyl orange as indicator, and then titrated with standard alkali, using phenolphtalein as indicator. Determinations of the phosphoric acid by independent methods indicated that the results were slightly below the truth.

Cavalier and Pouget[10] have studied the solubility of calcium glycerophosphate in water at various temperatures. They report that 1000 parts of a saturated, aqueous solution at 16° C. contain 7.9 gm. of the salt; at 36° the amount held in solution is 4.4 gm.; at 51°, 2.3 gm.; at 77°, 1.3 gm.; at 86°, 1.25 gm., and at 100°, 1.15 gm.

Eigelberner[11] prepared calcium glycerophosphate by the method used by Portes and Prunier. He estimated the calcium in an aqueous solution of the salt by precipitating as the oxalate, igniting and weighing as the oxide. The specimens which he prepared contained calcium equivalent to from 21.6 per cent to 22.5 per cent of calcium oxide, the theoretical quantity being 22.6 per cent of the calcium oxide. One commercial specimen of the salt yielded 33.05 per cent of calcium oxide.

Jensen[12] reports that he found a commercial specimen of the calcium salt which he believed to contain dicalcium glycerophosphate. By precipitation with ammonium oxalate in hot, very dilute acetic acid solution he obtained 23.5 per cent of calcium.

Except as chemical curiosities little attention was paid to the glycerophosphates until 1894, when they were introduced into medicine by Robin[13] in the belief that they were of value in malnutrition. Their use spread rapidly and it was not long before they were recommended in a variety of diseases. One or more of the glycerophosphates is described in nearly every foreign pharmacopoeia. The therapeutic value of the glycerophosphates has been questioned and conservative writers on materia medica no longer advocate their extended use.

Recent experiments[14] have shown that the animal organisms can build up lecithins, nucleoproteids and other phosphorus-containing compounds quite as readily from the inorganic phosphates as from organic phosphorus compounds. Hence it is probable that the glycerophosphates possess no therapeutic advantages over the inorganic phosphates.

The Council on Pharmacy and Chemistry having decided to consider calcium glycerophosphate, market specimens of different brands were purchased and were examined according to a number of provisional standards for the salt, which latter were chiefly based on the tests found in foreign pharmacopœias. These tests required the salt to be soluble in 30 parts of water. All but the merest traces of heavy metals were excluded. A limit test for carbonate, which permitted about

[9] J. pharm. chim. [6], 7, 5 (1898).
[10] Bull. soc. chim. [3], 21, 364 (1899).
[11] Am. Jour. Pharm., 76, 212 (1904).
[12] Evans' Analytical Notes, 6, 18 (1911).
[13] Bulletin acad. med. [3], 31, 419 (1894).
[14] Fingerling, G.: Die Bildung von organischen Phosphoverbindungen aus Phosphaten, Biochem. Ztschr., 1912, xxxviii, 448; McCollum, E. V., and Halpin, J. G.; Synthesis of Lecithins in the Hen. Proc. Am. Soc. Biol. Chem., 1911, Jour. Biol. Chem., 1912, xi, xiii.

1 per cent of a soluble carbonate, was described and limiting tests for sulphate and chloride were also given which permitted about 0.1 per cent each of sodium chloride and of calcium sulphate. The permissible acidity amounted to about 0.7 per cent of free acid, calculated as crystallized citric acid. The alcohol-soluble material was limited to 1 per cent, the loss on drying over sulphuric acid to 5 per cent, the ash between 52.5 per cent and 55.7 per cent, and the calcium between 16.5 per cent and 17.5 per cent. The calcium was determined by oxidation of the organic matter with nitric acid and potassium chlorate, neutralization of the solution with ammonia water, solution of the calcium phosphate in citric acid and precipitation of the calcium with ammonium oxalate test solution.

The results obtained in the examination with the exception of the tests for heavy metals and for carbonates which were negative in each case are tabulated herewith:

TABLE I*

| Brand | M. C. W. | P. W. R. | Schering | Squibb | Merck |
|---|---|---|---|---|---|
| Solution in Water (1 to 30) | Faintly Turbid | Very Turbid | Distinctly Turbid | Very Nearly Clear | Very Nearly Clear |
| Calcium | 12.73 | 15.60 | 15.71 | 14.48 | 14.18 |
| Chloride (NaCl) | 1.80 | 0.97 | Trace | Trace | Trace |
| Sulphate ($CaSO_4.2H_2O$) | Trace | 1.84 | 1.04 | 0.62 | 0.24 |
| Alcohol—Soluble | 0.66 | 0.73 | 3.52 | 6.34 | 4.47 |
| Cubic centimeters tenth—normal alkali required for 1 gm. of substance† | None | 4.47 | 6.06 | 12.86 | 13.66 |
| Loss over sulphuric acid | 4.47 | 3.54 | 3.23 | 2.91 | 2.99 |
| Residue on ignition | 51.93 | 51.01 | 50.69 | 47.72 | 47.84 |

All of these findings were submitted to each of the manufacturers whose product had been examined, but the key to the table of results was supplied to the individual manufacturer only so far as to enable him to identify his own product. At the same time each of the several firms was invited to criticize the tests in general and the findings for its own product.

While awaiting the criticisms of the manufacturers further experimental work was carried out on the calcium determination. It was found that by rendering the calcium glycerophosphate completely soluble by means of small quantities of citric acid, the calcium might be estimated with a fair degree of accuracy without the preliminary oxidation of the glycerophosphate. The method is given herewith:

From 0.3 gm. to 0.5 gm. of calcium glycerophosphate is weighed into a beaker, dissolved in 50 cc. of a 1 per cent. solution of citric acid, the solution filtered, 10 cc. of ammonium oxalate test solution added, the mixture warmed on the water bath for half an hour, allowed to stand for 24 hours, the precipitate of calcium oxalate collected, heated to low redness, cooled, the residue of calcium carbonate moistened with ammonium carbonate test solution, dried, again heated, and weighed.

In general the results obtained were slightly higher than those by the oxidation-

* The initials at the heads of the several columns correspond to the products sold by the following firms:
M. C. W.—Mallinckrodt Chemical Works.
P. W. R.—The Powers-Weightman-Rosengarten Co.
Schering—Schering & Glatz.
Squibb—E. R. Squibb & Sons.
Merck & Co.

† For the most part the acidity appears to be due to citric acid.

precipitation method. The determination of the amount of loss sustained by the salt when dried over sulphuric acid gave results that appeared to be of but little value in determining either the composition or the quality of the product. This test was evidently prescribed with the view of limiting the amount of adherent moisture rather than water of hydration. There is considerable confusion in the literature concerning the temperature at which the salt becomes anhydrous. Petit and Polonovsky, as noted earlier in this paper, prescribed a limit for loss on drying at 130° C., these chemists evidently believing that all of the water is driven off at that temperature. Astruc has reported that a temperature of from 150° C. to 160° C. is necessary for the determination of the water. The French Codex states that the salt becomes anhydrous at about 120° C. *but directs that the product shall be dried at* 150° *C. before analysis.* Hager (Handbuch Pharm. Prax., I, 96) states that the salt loses its water of hydration at 130° C. Concerning this we have made a few preliminary tests upon specimens containing little or no citric acid. These indicated that, after drying to constant weight at 130° C., no further loss took place if the temperature were raised at 150° C. As a drying temperature of 130° C. is thought by several of the authorities to be sufficient to drive off all the water of hydration and, as our preliminary tests appeared to confirm the belief, we chose that temperature and dried all of the specimens examined accordingly.

As the calcium content of the several specimens varied considerably it seemed worth while to determine the phosphorous also. This was carried out as follows:

From 0.3 gm. to 0.5 gm. of calcium glycerophosphate is weighed into a Kjeldahl flask, 10 cc. of a mixture of equal parts of nitric acid and sulphuric acid added, the mixture heated until oxidation is complete, a little more of the acid mixture being added with continued heating if necessary, the solution diluted with 50 cc. of water, 5 gm. of ammonium nitrate added, the mixture warmed, shaken and allowed to stand on the water bath until precipitation is complete, followed by 150 cc. of ammonium molybdate test solution, the precipitate dissolved in a slight excess of ammonia water, the solution filtered, 10 cc. of magnesia mixture test solution added, the mixture stirred, allowed to stand for 12 hours, the precipitate collected in a tared Gooch crucible, washed with 1 per cent. ammonia water, dried, heated to low redness for 15 minutes, cooled and weighed.

The results for calcium by the second method, for loss on drying at 130° C., and for phosphorus are given in the appended table:

TABLE II

| Brand | M. C. W. | P. W. R. | Schering | Squibb | Merck |
|---|---|---|---|---|---|
| Water (Loss at 130° C.) | 8.94 | 9.17 | 10.72 | 10.73 | 9.92 |
| Calcium | 12.84 | 15.83 | 15.65 | 15.21 | 14.95 |
| Phosphorus | 13.42 | 12.05 | 11.73 | 11.38 | 11.40 |

Pure calcium glycerophosphate, $Ca(C_3H_7O_6P.H_2O)$, should be soluble in water, should have a faintly alkaline reaction and should be practically free from chlorides, sulphates and alcohol-soluble matter. It should contain about 17.5 per cent of calcium and 13.6 per cent of phosphorus, and should yield about 55.7 per cent of ash on ignition. The results of the analysis show that none of the specimens examined were completely soluble in water. Those which were most nearly completely soluble were such as contained considerable quantities of an organic acid. The loss at 130° C. ranged from 8.9 per cent to 10.7 per cent, the theoretical loss for a salt containing 1 molecule of water of hydration being 7.9 per cent. Two specimens contained considerable amounts of chloride and four of them

contained considerable quantities of sulphate. One specimen (Powers-Weightman-Rosengarten brand) contained both chloride and sulphate. The alcohol-soluble material ranged from 9.66 per cent to nearly 7.5 per cent, the greater part of it, apparently being citric acid. The calcium content ranged from 12.6 per cent to 15.8 per cent, phosphorus from 11.4 per cent to 12.1 per cent, and the residue on ignition from 47.7 per cent to 51.9 per cent. The Mallinckrodt specimen contained considerable sodium. Since the calcium content of this specimen is considerably below the theory for calcium glycerophosphate and the phosphorus content is about normal for that salt, it appears probable that sodium glycerophosphate is present. In short, all of the specimens varied decidedly in one or more particulars. On comparing the results found in the examination with the standards prescribed in the foreign pharmacopœias and pharmaceutical commentaries it was found that none of the specimens examined complied with all of the requirements in any one of these authorities.

Concerning the tests suggested by us the several firms replied in general that the requirements were considered to be too stringent. Some believed that the standards extant in the foreign pharmacopœias and pharmaceutical commentaries were sufficient although, as we have already stated, our analyses had shown that none of the specimens examined complied with all of the requirements in any one of those authorities. Others stated that it was difficult to formulate standards of purity and strength for the substances because of the lack of uniformity in the commercial products. Still others thought that since the salt probably is to be described in the next revision of the U. S. Pharmacopœia, it was scarcely worth while to improve the product at this time.

From the Laboratory of the American Medical Association.

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Nature is very un-American. Nature never hurries. Every phase of her working shows plan, calmness, reliability, and the absence of hurry. Hurry always implies lack of definite method, confusion, impatience of slow growth. The Tower of Babel, the world's first skyscraper, was a failure because of hurry. The workers mistook their arrogant ambition for inspiration. They had too many builders,—and no architect. They thought to make up the lack of a head by a superfluity of hands. This is a characteristic of hurry. It seeks ever to make energy a substitute for a clearly defined plan,—the result is ever as hopeless as trying to transform a hobby-horse into a real steed by brisk riding.—*William George Jordan.*