NOTES ON THE WATER OF CRYSTALLIZATION OF QUININE SULPHATE.*[1]

BY GEORGE DENTON BEAL[2] AND CHESTER R. SZALKOWSKI.[3]

INTRODUCTION.

According to U. S. P. X, quinine sulphate contains "7 or 8 H_2O," and "effloresces rapidly when exposed to dry air or when heated to 50° C., losing all but two molecules of its water of crystallization and becoming lusterless." Among the "Tests for purity," we read: "Quinine sulphate loses not more than 16.2 per cent when dried to constant weight at 100° C. (*water*)."

Inquiry among pharmacists developed the fact that the U. S. P. description, rubric and directions for storage in well-closed containers were not regarded as of serious moment. As a matter of fact, this instability of the water of crystallization is seldom mentioned in pharmaceutical literature. Cownley[4] says that while it is generally stated that anhydrous quinine sulphate is only obtained at temperatures exceeding 110° C., his carefully controlled experiments show that the salt readily became anhydrous at 100° C., and that when freely exposed to the air in the anhydrous state it rapidly absorbs water to become a dihydrate. The freshly crystallized salt contains 7 to 8 molecules of water, and when exposed to the air it rapidly effloresces to the dihydrate.

H. B. Parsons[5] reported the water of crystallization of 1015 samples of quinine sulphate as determined by him. One Gm. of each was dried in the water oven for three hours with the following results:

Brand.	No. Samples.	Average Percentage Moisture.
American	16	13.72
American	184	12.61
German	12	12.32
German	634	14.19
Italian	169	14.36

Each sample reported represented 100 ounces from a previously unopened can. The differences above noted in the water of crystallization in the five brands reported were said to be tolerably constant and characteristic for each brand.

W. A. Spalding[6] weighed the contents of two quinine sulphate containers and repeated the weighings at intervals extending over twelve months for the first and eight months for the second. He observed a constant loss, 8 to 9 per cent for the first and 11.39 per cent for the second.

F. A. Thompson[7] found an average moisture content of 11.74 per cent in 183 samples, all of which responded to the other U. S. P. tests for purity.

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[2] Assistant Director, Mellon Institute of Industrial Research, Pittsburgh, Pa.

[3] Assistant in Research in Pure Chemistry, Mellon Institute.

[4] *Pharm. J. Trans.* (Sept. 2, 1876), 189.

[5] PROCEEDINGS, A. PH. A., 32 (1884), 457.

[6] *Ibid.*, 34 (1886), 605.

[7] *Ibid.*, 40 (1892), 267.

C. E. Sage[1] obtained two one-ounce bottles, one of which was opened and a little removed from time to time throughout two years, the other bottle kept sealed, and the two stored side by side. When finally assayed, the opened bottle contained 3.76 per cent of water while that in the sealed bottle contained 13.28 per cent. He also states that globules of water have been found condensed on the walls of tins containing quinine sulphate.

Reference has occasionally been made to original packages of quinine sulphate that were apparently under weight, or slack-filled. Comments have also been passed upon a change in appearance of the salt, whereby the long flaky crystals, so popular with those who gage their dose by apparent volume, have changed their form to short needles that have almost the appearance of a fine powder. Instances are also known where inspectors having prescriptions filled for subsequent analysis and possible prosecution have found said prescriptions as compounded to contain an unduly large amount of quinine, as much as 13 per cent in excess of the prescribed quantity being reported. The previously published articles suggest that these conditions are due to the ready loss of water of crystallization from quinine sulphate. We have been interested in determining the conditions and extent of this loss, and wish to report in part our studies to date.

EXPERIMENTAL.

Through the courtesy of C. Leonard O'Connell, of the Pittsburgh College of Pharmacy, and E. Fullerton Cook, of the Philadelphia College of Pharmacy and Science, Samples 1 to 15 were obtained from drug stores in Pittsburgh and 16 to 26 from the various laboratories of the Philadelphia College of Pharmacy. Samples 27 and 28 came from recently purchased, unopened containers obtained by the Department of Research in Pure Chemistry at Mellon Institute. Samples of approximately 1 Gm. were accurately weighed from tightly stoppered weighing bottles into tared porcelain dishes and dried in an electric oven at 100° C. until the weights became constant. The dishes were removed to desiccators for cooling at the end of two hours, weighed and returned to the oven to be reheated for another hour. No change in weights was observed as a result of the second drying.

TABLE I.—WATER OF CRYSTALLIZATION IN COMMERCIAL QUININE SULPHATE.

Sample No.	Description.	Per Cent Water.	Molecules Water.
1	From 1-oz. container. Very fine powder	4.39	1.9
2	Stock bottle. Very fine, glistening crystalline powder	5.73	2.5
3	Stock container. Fine silky needles	10.90	5.0
4	New container. Fine silky needles	9.66	4.4
5	Stock bottle. Very fine, silky needles	8.34	3.7
6	Stock bottle. Very fine, glistening powder	5.04	2.3
7	Stock bottle. Very fine, glistening powder	5.72	2.4
8	Glass-stoppered bottle. Very fine, glistening needles	7.45	3.3
9	Freshly opened can. Fine silky needles	12.27	5.8
10	Open stock container. Fine glistening powder	5.09	2.4
11	Open stock container. Fine glistening powder	4.69	2.0
12	Stock bottle. Fine glistening powder	4.61	2.0
13	Stock container. Fine glistening crystalline powder	6.56	2.9
14	Stock container. Fine glistening powder	4.72	2.0

[1] *Pharm. J.*, 119 (1927), 264.

15	Opened stock container. Very fine, silky needles	5.94	2.6
16	Original unopened container. 2 years old. Fine silky needles	4.77	2.1
17	Original unopened container. 2 years old. Fine silky needles	4.94	2.0
18	Stock bottle. Old. Fine glistening powder	4.57	1.9
19	Stock bottle. Old. Fine glistening powder	4.64	2.0
20	Stock bottle. Very fine, silky needles	5.19	2.2
21	Stock bottle. Fine silky needles	5.22	2.3
22	Original container. Opened 1 month. Very fine, silky needles	10.67	4.9
23	Original container. Unopened. Fine silky needles	10.78	5.0
24	Original container, screw cap. Fine silky needles	9.65	4.4
25	Original container. Unopened. Fine silky needles	5.78	2.5
26	Stock bottle. New. Fine silky needles	7.35	3.2
27	New 50-oz. can. Silky, glistening crystals	12.20	5.7
28	Five-oz. metal can. Six months old. Unopened. Fine silky powder	4.63	2.0
27-B	Sample 27 in glass-stoppered bottle 2 weeks. Fine glistening crystals	11.60	5.4
28-B	Sample 28 in lightly stoppered bottle 2 weeks. Fine silky powder	4.66	2.0

Samples of anhydrous quinine sulphate and of quinine sulphate octahydrate were prepared from Sample 28. The anhydrous sample was prepared by drying to constant weight in an oven at 100° C. A portion of the anhydrous salt was dissolved in boiling distilled water and the solution allowed to cool slowly, when the salt crystallized. The mother liquor was separated from the crystals on a Büchner funnel, the wet crystals transferred to a porcelain dish and partially dried at about 80° C. The dish was then cooled for one hour in a desiccator over 1:1 sulphuric acid. A sample of about 1 Gm. lost about 50 per cent in weight when dried at 100° C. The bulk of the crystals was returned to the oven at 80° C. for thirty minutes, cooled, the moisture determined, and these operations repeated until 16.78 per cent of water remained, corresponding to approximately 8.4 molecules. The mass of crystals was thoroughly mixed before sampling for subsequent experiments. The anhydrous sample will be designated hereafter as "A" and the recrystallized sample as "R."

The stability of the water of crystallization and the tendency of the salt to absorb water were determined by exposing weighed portions of 27-B, 28-B, A and R to various humidities, at laboratory temperature, 23° to 25° C., until the weights of the various portions became constant. The test portions were exposed in flat dishes in desiccators containing concentrated sulphuric acid, 3:1 sulphuric acid, 2:1 sulphuric acid, 1:1 sulphuric acid, saturated solution of potassium acetate (20 per cent humidity), saturated solution of calcium chloride (30 per cent humidity), saturated solution of potassium carbonate (40 per cent humidity), and saturated solution of ammonium chloride (80 per cent humidity). All samples were exposed to their particular atmosphere for three hundred and thirty-six hours, or fourteen days, and were weighed daily. In no instance was there any pronounced change after the ninth day.

The percentage loss in weight of these samples is given in Table II. The figures in the first line for each sample indicate the percentage loss of weight at that particular humidity (gain in weight with Sample A). The second line of figures represents the result of the subsequent moisture determination, heating at 100° C. for two hours. The third line of figures, for Samples R, 27-B and 28-B,

represents the total loss in weight of the sample, or, in other words, its water of crystallization.

TABLE II.—DETERMINATION OF WATER OF CRYSTALLIZATION OF QUININE SULPHATE AT VARIOUS HUMIDITIES.

Sample.	Original Water.	Lab. Hum. %	H_2SO_4 %	3:1 H_2SO_4 %	2:1 H_2SO_4 %	1:1 H_2SO_4 %	20% Hum. %	30% Hum. %	40% Hum. %	80% Hum. %
A	0	+ 4.95	+ 1.15	+ 4.15	+ 4.63	+ 4.68	+ 5.15	+ 5.18	+ 5.11	+ 5.10
		− 4.97	− 1.33	− 4.00	− 4.61	− 4.76	− 5.15	− 5.22	− 5.17	− 5.22
R	16.78	−10.60	−11.90	−11.85	−11.68	−11.15	−11.12	−11.70	−10.52	− 3.38
		− 5.00	− 4.78	− 5.08	− 5.20	− 4.96	− 5.01	− 5.14	− 6.28	−13.50
		−15.60	−16.68	−16.93	−16.88	−16.11	−16.13	−15.84	−16.80	−16.88
27-B	11.60	− 6.70	− 6.98	− 6.88	− 7.00	− 6.50	− 7.20	− 7.05	− 6.66	− 2.68
		− 5.12	− 4.59	− 4.88	− 5.18	− 4.51	− 5.25	− 5.10	− 5.76	− 9.15
		−11.82	−11.57	−11.76	−12.18	−11.01	−12.45	−12.15	−12.42	−11.83
28-B	4.66	− 0.04	− 0.03	− 0.07	− 0.005	− 0.002	0.00	0.00	0.00	0.00
		− 5.30	− 4.80	− 5.06	− 5.03	− 5.21	− 4.05	− 4.48	− 5.34	− 5.48
		− 5.34	− 4.83	− 5.13	− 5.035	− 5.212	− 4.05	− 4.48	− 5.34	− 5.48

\+ Indicates increase in weight.
− Indicates loss in weight.

CONCLUSIONS.

Although some discrepancies appear in the preceding table, these particular determinations have not been repeated, as our purpose at this time has only been to determine the trend of the dehydration or hydration.

Examination of the data in Tables I and II will indicate the tendency of this salt to form a stable dihydrate. The per cent of water in the dihydrate is 4.60, in the heptahydrate 14.43, and in the octahydrate 16.16. This tendency is in agreement with the U. S. P. description, which states that when exposed to dry air or when heated to 50° C. it loses all but two molecules of its water of crystallization.

The tendency of quinine sulphate U. S. P. to dehydrate is marked, and it behooves pharmacists to buy quinine sulphate only in small, tightly closed containers, to store them in a cool place, and to keep the packages tightly and imperviously stoppered between the occasions of their use.

Quinine sulphate of less than U. S. P. water content may be easily converted to the dihydrate by exposure to dry air or by heating at 50° C.

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THE DETECTION OF SMALL QUANTITIES OF CARBON MONOXIDE IN MEDICINAL OXYGEN.*

BY JACOB E. SCHMIDT AND JOHN C. KRANTZ, JR.

INTRODUCTION.

The detection and quantitative determination of small quantities of carbon monoxide in air and blood have been the subject of much investigation during the last three decades. However, little attention has been centered on the detection

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