

The results with α -ethyl cinnamic N-ethyl amide support the belief that low resorbability is an important factor throughout the series. In this compound it would be expected that both the hypnotic potency and the toxicity should be increased and that the therapeutic ratio potency/toxicity should be decreased. The facts are (1) that the therapeutic ratio decreased greatly so that the hypnotic dose equalled the lethal dose; and (2) that the absolute values of both the potency and toxicity decreased. These facts seem explainable only if it be assumed that only a small part of the dose was resorbed.

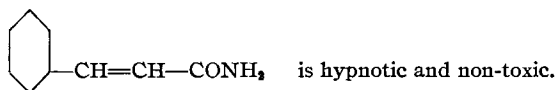
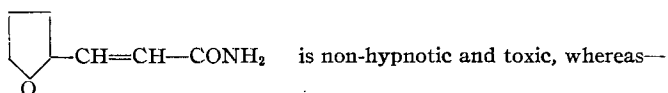
The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

1. An extensive series of ureides and amides derived from the substituted acrylic acids were prepared. A large number of these acids were substituted β -phenyl acrylic or cinnamic acids. One example of a β -heterocyclic acrylic acid, *viz.*, furfuracrylic acid, was included.

2. The biological results with rats seem to indicate that the whole series of compounds were characterized by low resorbability and that the ureide series were further characterized by rapid intestinal hydrolysis. This rapid intestinal hydrolysis seems to be shared by the amide series in the intestine of higher animals (dog). The net hypnotic action and toxicities were, therefore, quite low.

3. The furane ring is considerably more toxic than the benzene ring, and contributes no characteristic hypnotic action, so that in practical terms—



REFERENCES.

- (1) Delepin and Bonnet, *Compt. rend.*, 149 (1909), 39.
- (2) Bogert and Davidson, *J. A. C. S.*, 53 (1931), 3122.
- (3) "Organic Syntheses," Vol. 9, page 38, J. Wiley, New York.
- (4) Nieuwland and Daig, *J. A. C. S.*, 53 (1931), 1842.

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THE WATER OF CRYSTALLIZATION OF QUININE SULPHATE.*

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Quinine sulphate crystallized from water has been variously reported as containing 7 and 8 molecules of water. It has also been reported that when exposed

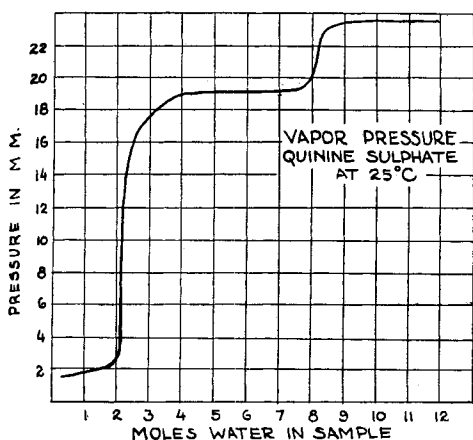
* Scientific Section, A. PH. A., Washington meeting, 1934.

¹ Drug Control, Food and Drug Administration.

to the air it loses water until the dihydrate is formed. (Hesse, *Annalen*, 166 (1873), 217; 176 (1875), 213; Beal and Szalkowski, *JOUR. A. PH. A.*, 22 (1933), 1219.) In all of the experiments reported, the water content has been determined by drying the quinine sulphate in an oven to constant weight. Such tests while showing the amount of water which the quinine sulphate contains do not show how much, if any, exists as water of crystallization, and how much is simply absorbed or dissolved in the quinine sulphate.

It is well known that any water-soluble substance when exposed to the air takes up or loses water until the vapor pressure of the solid solution is equivalent to the pressure of the water vapor in the atmosphere. One method of determining the manner in which the water in a product is held is to measure the change in vapor pressure as small increments of water are removed at a constant temperature.

Theoretically, if water is progressively removed from a hydrate the vapor pressure at a constant temperature remains constant as long as any of that hydrate remains. At this point the pressure drops to that of a lower hydrate, if one is present, or to that of the anhydrous substance. In practice, however, these breaks are not always sharp. Beutell and Blaschke (*Centr. Mineral. Geol.*, 1915, 199) found that in all cases where there is more than one hydrate, the dehydration on



the surface of the particles proceeds further than in the interior "where cohesion hinders the evolution of water vapor." The inside of the particles, therefore, may consist of hydrates higher than those at the surface. This prevents a sharp transition from one hydrate to the next and causes the break to become rounded in the plotted curve. This rounding becomes more pronounced the greater the pressure difference between two hydrates.

On the other hand when dealing with a compound in which the water is not present as a hydrate the pressure drops as the water is removed. The curve showing the relation of vapor pressure to water content will not have the breaks characteristic of the hydrate curves, but will be perfectly smooth, its slope being determined by the tenacity with which the water is held.

METHOD.

Quinine sulphate was recrystallized from water and a weighed quantity of the wet crystals used for the determination. Wet quinine sulphate was used in order to avoid any partial desiccation of the highest hydrate. The apparatus used was that described by Wales and Nelson (*J. Am. Chem. Soc.*, 45 (1923), 1657). The product to be tested was placed in a glass bulb sealed to a manometer. A tube containing phosphoric anhydride was placed between this apparatus and the vacuum pump. The system was evacuated for a few seconds, the stop-cock between the drying tube and the manometer system closed and the pressure permitted to come to equilibrium before readings were taken. By this method the vapor pressure was determined to ± 0.5 mm. By weighing the phosphoric anhydride tube after each evacuation the amount of water removed was deter-

mined. The total quantity of water in the quinine sulphate was determined from the total gain in weight of the tube containing phosphoric anhydride. In order to insure complete dehydration the last traces of water were removed by long evacuation at 100° C.

The accompanying table and chart show the results obtained at 25° C. using this method. The highest portion of the curve is approximately the vapor pressure of water at 25° C. and represents the excess moisture since a wet sample was used. The breaks in the curve correspond to 8 and 2 moles of water showing the existence of an octohydrate having a vapor pressure of 19.3 mm. at 25° C. and a dihydrate having a vapor pressure of approximately 2 mm. at the same temperature. No evidence of a heptahydrate is shown. Due to the fact that the apparatus used was not capable of determining pressures below 2 mm. with any degree of accuracy the possibility of a third hydrate having less than two molecules of water of crystallization has not been precluded.

VAPOR PRESSURE AT 25° C. OF QUININE SULPHATE CONTAINING VARYING AMOUNTS OF WATER.

Water in Sample, Per Cent.	Moles Water in Sample.	Pressure, Mm.	Water in Sample, Per Cent.	Moles Water in Sample.	Pressure, Mm.
19.36	10.31	23.5	9.78	4.49	19.0
19.18	9.83	23.5	8.02	3.93	19.0
18.36	9.32	23.2	7.69	3.45	18.4
17.71	8.92	23.0	7.13	3.18	18.0
16.86	8.40	23.0	6.49	2.88	17.0
16.22	8.02	20.0	5.87	2.58	16.5
15.33	7.50	19.8	5.25	2.29	14.0
13.85	7.00	19.3	4.92	2.15	8.5
13.66	6.56	19.3	4.84	2.11	4.6
13.02	6.20	19.5	4.78	2.08	2.2
12.25	5.79	19.2	2.51	1.10	1.8
11.56	5.42	19.1	1.02	0.43	1.6
10.74	4.98	19.0			

As stated above, quinine sulphate when exposed to the air takes up or loses water until its vapor pressure is in equilibrium with the vapor pressure (humidity) of the air in the room. Since the octohydrate has a vapor pressure close to that of water (corresponding to a humidity of about 82% at 25° C.) it will lose water unless exposed to very moist air. The dihydrate on the other hand would be in equilibrium with the air only under desert conditions. Inspection of the accompanying curve shows that under ordinary conditions equilibrium with water vapor in the air will be reached somewhere on the sharp break in the curve and that quinine sulphate stored in an open container will contain slightly more than 2 moles of water.

CONCLUSIONS.

By means of vapor pressure measurements it is shown that the water content of quinine sulphate is present as water of crystallization. Quinine sulphate crystallizes from water at room temperature with eight molecules of water of crystallization. This is not stable when exposed to the air and is transformed to the dihydrate. No evidence of quinine sulphate containing seven molecules of water of crystallization was found.