

SUMMARY AND CONCLUSIONS.

1. From this study it appears that although the guinea-pig method of assay is now official, tinctures of aconite now offered for clinical use still show great variation in physiological activity.

2. There exists a close relationship between stability and hydrogen-ion concentration, as had previously been shown by Swanson. In view of this it would seem highly desirable that, if the preparation is to be retained in the Pharmacopœia, the product should be adjusted to the proper p_H as recommended by Swanson.

3. As in the case of all drugs subject to deterioration, a statement should be made on the labels of these preparations giving the date of manufacture and the time limit, if possible, beyond which the drug should not be used.

4. Inasmuch as it has been shown that digitalis leaf is far more stable than any of its liquid preparations (16) it would seem desirable that studies be made to ascertain whether the same holds true for aconite.

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DEPARTMENT OF PHARMACOLOGY,
MEDICAL COLLEGE OF VIRGINIA,
RICHMOND, VA.

THE HYDROLYSIS OF ARSENOUS IODIDE.***

BY WILLIAM J. HUSA.***

Reference books differ in their statements regarding the rate and extent of hydrolysis of arsenous iodide in aqueous solution. Hager's "Handbuch" (1) states that the aqueous solution is neutral, and that on long standing, or more rapidly on heating or in concentrated solution, hydriodic acid and arsenous acid appear in the solution. According to the U. S. P. (2), "one Gm. of arsenous iodide is soluble in about 12 cc. of water at 25° C. with partial decomposition" and "a freshly prepared aqueous solution of the salt is colorless, but upon standing, it

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*** Professor of Pharmacy, University of Florida.

gradually decomposes with the formation of arsenous and hydriodic acids and becomes yellow due to the liberation of iodine." The British Pharmacopœia (3) indicates that "the aqueous solution is acid to litmus—."

In the present study, a search of the literature was made to find out what foundation there was for the statements quoted above, and experiments were carried out to determine the rate and extent of hydrolysis of arsenous iodide in aqueous solution.

HISTORICAL REVIEW.

At a meeting of the "*Société de Pharmacie de Paris*" in December 1827, A. Plisson reported (4) that arsenous iodide had been prepared by heating together the free elements in accordance with the directions of M. Henry, chef de la pharmacie centrale, for use as an external remedy by M. Biett, docteur médecin de l'hôpital Saint-Louis. On this occasion Plisson also gave directions for the preparation of the triiodide by the action of arsenic on iodine in the presence of water. He further reported that the solution of arsenous iodide was capable of dissolving mercuric iodide, thus antedating by 12 years the observation (5) of Dr. M. Donovan of Dublin.

For a year thereafter the meetings of the society were enlivened by a controversy regarding the nature of aqueous solutions of arsenous iodide. Sérullas and Hottot (6) pointed out that one would expect AsI_3 to hydrolyze in water as in the case of SbI_3 , $SbCl_3$ and $AsCl_3$. They considered the solution of arsenous iodide in water as a mixture of hydriodic acid and arsenous oxide, citing as proofs the fact that the solution turned litmus red very strongly and that HI could be separated by distillation. Plisson (7) contended that the solution contained the elements of the iodide, not simply mixed in the state of the acid and the oxide, but well combined in the form of the iodide or "neutral hydriodide." One reason he gave in support of his views was that the solution had a yellowish color, and that it was thus not colorless as it would be if it represented only a mixture of the acid and oxide. After about a year of research and debate, the controversy was dropped, with both factions still fully confident of the correctness of their views.

Donovan (5), in 1839, evidently thought that water did not decompose arsenous iodide, since he considered that his solution of arsenous iodide and mercuric iodide contained a double iodide of arsenic and mercury. However, in the following year, Bette (8) observed that the aqueous solution of arsenous iodide showed an acid reaction. In 1859, Nicklès (9) reported that in contact with water, arsenous iodide decomposes into arsenous acid and hydriodic acid.

A few years later, the idea that the hydrolysis of arsenous iodide is a gradual process began to appear in reference books, although there seems to be no original work in the literature to support this view. The U. S. P. of 1870 (10) stated that the solution is gradually decomposed on standing, and that arsenous iodide is gradually decomposed by boiling water.

In 1881, Bamberger and Philipp (11) said that the solution undoubtedly contains hydriodic acid and arsenous acid. Since even Plisson (7) had recognized that the solution of arsenous iodide reddened litmus, and in view of the fact that all workers up to this point who mentioned the reaction of the solution had agreed that it was acid in reaction, it is difficult to see why some of the reference books

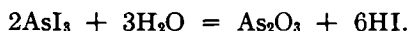
of this period began to include the statement that the solution is neutral in reaction. Thus in the "National Dispensatory" of 1884 (12) we find the statement that arsenous iodide "is soluble, with a neutral reaction and without decomposition, in water, alcohol, ether and carbon disulphide, but is gradually decomposed on being boiled with water or alcohol." The U. S. P. VIII stated that the solution is neutral to litmus paper and that it gradually decomposes on standing. According to the U. S. P. IX and U. S. P. X, arsenous iodide dissolves with partial decomposition, with further gradual decomposition on standing.

While the reference books were following the trends indicated above, the idea that arsenous iodide is practically completely hydrolyzed was expressed from time to time by various investigators, including Dott in 1893 (13), Dupouy in 1901 (14), Duncan in 1903 (15), Langenhan in 1925 (16) and Husa and Enz in 1929 (17).

However, during the one hundred years from 1828 to 1928, no real advance was made over the original observations and conclusions of Sérullas and Hottot (6). During this long period no exact quantitative measurements were made which would give an exact knowledge of the extent to which arsenous iodide is hydrolyzed in aqueous solution.

EXPERIMENTAL PART.

In the present investigation, it was planned to make accurate measurements of the p_H of solutions of arsenous iodide, by use of the quinhydrone electrode. While this work was in progress, an article was published by Cocking (18) in which data were presented on the point in question. According to Cocking "The hydrolysis of arsenous iodide in a freshly made dilute solution is almost complete, the reaction of an aqueous solution containing 1.52 per cent of the salt (approximately decinormal), being about p_H 1.1, that is, the same as that of a decinormal solution of hydriodic acid. Therefore it must be assumed that arsenous iodide dissolved in water is at once almost completely hydrolyzed into arsenious and hydriodic acids.



The dissociation constants of arsenious acid

$$K_a 6 \times 10^{-10}, K_b 1 \times 10^{-14}$$

being very small have no appreciable effect on the p_H of dilute solutions."

Although the excellent report of Cocking seemed fully acceptable, the work under way was continued with the idea of verifying the results and in order to determine whether any further change occurs on standing.

Measurements with Quinhydrone Electrode.—Cocking (18) has given no information as to his method of determining the p_H . In the present study, measurements were first made using the quinhydrone electrode. It was found that the addition of the quinhydrone caused an immediate liberation of free iodine, thus vitiating the results. Attempts to stabilize the solution by adding a few drops of hypophosphorous acid or 1 Gm. of dextrose to 35 cc. of solution proved unsuccessful. It was concluded that the quinhydrone electrode was not applicable to solutions containing hydriodic acid.

Measurements with Indicators.—As the solutions to be tested were clear and practically colorless, it seemed that indicator methods should give good results. Ac-

cordingly, determinations were made, using the La Motte block comparator and color standards, the indicators employed being acid cresol red and meta cresol purple. A solution of arsenous iodide containing 1.52 Gm. per 100 cc. was prepared. Ten minutes after mixing the ingredients a portion of the mixture was filtered while still slightly turbid. (When mixed with water the AsI_3 lost its brick-red color and became white, due to hydrolysis. The turbidity was due to undissolved As_2O_3 or basic salt.) The p_{H} of this solution was found to be 1.1. Half an hour after mixing the ingredients the solution was practically clear and showed a p_{H} of 1.1. After 3 hours the solution was entirely clear and the p_{H} was 1.1. Likewise after 1 day and after 25 days the p_{H} was still 1.1.

For the sake of completeness the p_{H} of $N/10$ HI as given by Cocking was verified. The HI (for the preparation of which I am indebted to Mr. Paul S. Shattuck) was made by passing H_2S into a mixture of iodine and water until the iodine was decolorized, filtering out the sulphur, and distilling *in vacuo*. By this method a pure, colorless solution of HI was obtained, which was diluted to make a tenth-normal solution. The p_{H} was 1.1. The above results confirm the work of Cocking, and also show that there is no further change in p_{H} in 25 days.

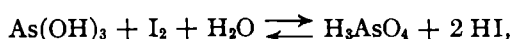
Measurements on Donovan's Solution.—Donovan's Solution was prepared from two different lots of arsenous iodide, using the same kind of mercuric iodide in each case. One solution showed a p_{H} of 1.3 immediately after preparation, and after 1 day and 25 days the p_{H} was still 1.3. The other solution had a p_{H} of 1.2 immediately after preparation, and there was no change after 1 day and 25 days. With this particular lot of arsenous iodide there was practically no residue in the preparation of Donovan's solution, while with the other lot there was considerable residue to be removed by filtration. These results indicate that the p_{H} of Donovan's solution may vary slightly with the materials used, but after it is prepared there is no further change in the next 25 days.

DISCUSSION OF RESULTS.

The results indicate that a dilute aqueous solution of arsenous iodide is essentially a solution of arsenous acid and hydriodic acid, in equilibrium with a small proportion of arsenous iodide, the amount of the latter being necessarily comparatively small in view of the p_{H} .

It is clear that as a practical matter, time is not a factor in the hydrolysis, since even in freshly prepared solutions, equilibrium is reached in the few minutes necessary for the measurements to be made. The statement (1) that the aqueous solution is neutral is quite evidently erroneous.

In the next revision of the U. S. P. the statement regarding "partial decomposition" should be changed. Also since solutions of arsenous iodide have a characteristic pale yellowish color, and since free iodine will not appear until equilibrium has been reached in the following equation:



it is suggested that the U. S. P. XI monograph should read as follows:

"One Cm. of Arsenous Iodide is soluble in about 12 cc. of water at 25°C ., with almost complete hydrolysis to arsenous and hydriodic acids. It is soluble in alcohol, chloroform, ether and carbon disulphide.

"A freshly prepared solution of the salt is colorless or pale yellowish; upon standing, after most of the arsenic has been oxidized to the pentavalent form, it becomes yellow due to the liberation of iodine."

SUMMARY.

1. A dilute aqueous solution of arsenous iodide is essentially a solution of arsenous acid and hydriodic acid, in equilibrium with a small proportion of arsenous iodide.
2. As a practical matter, time is not a factor in the hydrolysis at arsenous iodide, since in freshly prepared solutions equilibrium is reached within a few minutes.
3. Definite suggestions are presented as to necessary changes in the U. S. P. monograph.

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ABSTRACT OF DISCUSSION.

James C. Munch asked whether the author knew the percentage of arsenic and iodine in the solution, *i. e.*, Arsenous Iodide. The author replied this could be determined.

H. A. B. Dunning inquired whether there was a way of preventing hydrolysis. The author knew of no way of preventing it.

COLLEGE OF PHARMACY,
UNIVERSITY OF FLORIDA,
GAINESVILLE, FLA.

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