THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

THE MANUFACTURE OF DILUTED HYDRIODIC ACID. A DEMONSTRATION AT THE LABORATORY CONFERENCE.*

BY SAMUEL SHKOLNIK.

The instruction given in the manufacturing laboratory at the University of Illinois School of Pharmacy correlates the work for the student, for if the student is left to do this for himself he may not use the information so as to intelligently carry out his practice of Pharmacy. The method which is employed by Prof. Clyde M. Snow is to present in lecture form the theoretical discussions of preparations which are to be actually manufactured the week following in the pharmaceutical laboratory. These theoretical lectures are presented twice a week and in every case, when possible, actual demonstrations of the chemical reactions and of the processes of manufacturing in general are made at the lecture stand. Such an arrangement gives the student an opportunity to review the lecture notes and study the preparation which is to be manufactured in the laboratory.

Although a practical demonstration at the lecture stand impresses the student, his attention is held only temporarily and it is therefore advisable and even necessary to precede the manufacturing exercise in the pharmaceutical laboratory by a detailed discussion of the process, chemical reactions and technic involved. Such preliminary discussion fills about an hour, after which follows a three-hour period of actual manufacturing work.

As a teaching demonstration at this laboratory conference I selected the discussion of the manufacture of Diluted Hydriodic Acid, which is a preparation manufactured by our freshmen students and one which is typically outstanding from a pharmaceutical chemistry standpoint, because of the particular ingredients used and the chemical changes involved in its manufacture. During the first hour of the preliminary discussion one student is called upon to read before the class from the laboratory manual the official formula and method of preparation of Diluted Hydriodic Acid. This alone, however, does not inform the class of the "Whys" and "Hows" and if left to go on with the exercise the students would merely be following the directions outlined without any scientific visualization— thus lacking the essential element which distinguishes the educated pharmacist from the so-called pharmacist.

Originally, Diluted Hydriodic Acid was prepared by passing Hydrogen Sulphide into Iodine and water according to the following equation: $2I_2 + 2H_2S = 4HI + S_2$. Andrew Buchanan of Glasgow prepared Diluted Hydriodic Acid extemporaneously by dissolving Tartaric Acid and Potassium Iodide each in water and mixing the two solutions and filtering and adding enough water so that each fluid drachm contained the equivalent of 5 grains of Iodine. Dunn's later modification was to cool the mixture and add enough water so that each fluid drachm contained the equivalent of 10 grains of Iodine. The present U. S. P. method is based on the old Buchanan process with some modifications.

---

* Presented before the Section on Pharmacy of the American Association of Colleges of Pharmacy, Philadelphia, September 1926.

The U. S. P. X formula for Diluted Hydriodic Acid calls for 135 Gm. of Potassium Iodide to be dissolved in 250 cc. of distilled water and 122 Gm. of Tartaric Acid to be disolved in 400 cc. of Diluted Alcohol. These two solutions are then mixed well and cooled at 5° C. for 2 hours. Upon mixing the two solutions double decomposition takes place between the tartaric acid or hydrogen tartrate and the KI producing hydrogen iodide and potassium acid tartrate or potassium bitartrate as an insoluble by-product according to the following equation: $KI + H_2C_4H_4O_6 = HI + KHC_4H_4O_6$. The HI itself is a heavy gaseous compound which disolves in the water present and forms Hydriodic Acid. The above reaction goes to completion because the by-product potassium acid tartrate is an insoluble salt and, of course, is precipitated as fast as formed, particularly so when the liquid is alcoholic and cold; hence the explanation for cooling the mixture of the two solutions for 2 hours. This reaction will go to completion whenever one of the products formed is an insoluble and hence un-ionizable substance.

The HI formed ionizes into positive hydrogen ions and negative iodine ions, but the potassium bitartrate being insoluble does not ionize and, therefore, there are no potassium ions in solution which could combine with the iodine ions and no tartrate radical ions which could combine with hydrogen ions and cause the reaction to reverse; hence all the potassium is precipitated as potassium bitartrate or potassium acid tartrate which is removed by the process of filtration and all the iodine remains in solution in the form of hydrogen iodide.

The question that usually arises at this point is, could HI be made from any other iodide than KI? Here the student ordinarily seeks a "cut and dried" unqualified answer. But it is another one of those cases where neither "Yes" nor "No" without any further qualifications will suffice as a satisfactory answer. While HI could be prepared from any other soluble iodide, such as sodium or lithium iodide, KI is used because the resulting by-product is insoluble and can be readily removed by filtration which would not be the case if sodium or lithium iodides were used, for the bitartrate of these metals is soluble. Similarly, in reply to the question whether HI could be made from any acid other than tartaric the same explanation could be advanced, that is—any acid which will react with the KI will furnish HI but tartaric acid is selected because the tartrate radical, combining with the potassium from the KI, forms an insoluble potassium salt, namely potassium bitartrate; all other salts of potassium are soluble and, therefore, no other acid radical would form an insoluble by-product with the potassium. Of course, the use of sulphuric acid would be objected to on two grounds: First the by-product formed would be potassium sulphate or potassium acid sulphate, as the case may be, both of which are soluble and, therefore, could not be separated by filtration. Second, sulphuric acid, being an oxidizing agent, would oxidize the HI as fast as formed, liberating free iodine by changing the valence of sulphur from $+6$ to $+4$, $+2$, or even neutral, and raising the valence of Iodine from -1 to 0.

Having explained why the two particular chemicals KI and tartaric acid were chosen there remains another peculiarity which should not be overlooked and that is the different solvents used. We know that KI is rather insoluble in alcohol (1:25) or alcoholic liquids but is readily soluble in water (1:0.7), hence the explanation for dissolving the KI in water. But we also know that tartaric

acid is soluble in both water and alcohol and now the question arises why is the tartaric acid dissolved in Diluted Alcohol and not in water, as such, or alcohol, as such? Understanding that the KI is rather insoluble in alcohol we could reasonably expect that if the tartaric acid were dissolved in alcohol, as such, and mixed with the aqueous solution of KI, a portion of the KI, at least, would be thrown out of solution and result in a deficiency of HI to be produced. On the other hand the introduction of alcohol is desirable to completely precipitate the by-product—potassium bitartrate—which is more insoluble in alcoholic liquids than it is in aqueous; hence, the explanation for dissolving the tartaric acid in Diluted Alcohol which, being alcoholic, aids in the precipitation of the potassium bitartrate and yet it is not too strongly alcoholic to throw out potassium iodide from solution.

A similar explanation is offered for washing the precipitate of potassium bitartrate with Diluted Alcohol, that is, the HI which is retained by the precipitate (and for the purpose of obtaining it the precipitate is washed) is dissolved out by Diluted Alcohol without carrying with it any of the undesirable potassium bitartrate as would probably be the case if water alone were used; for the insolubility of potassium bitartrate is greater in alcoholic liquids than in aqueous.

Since the introduction of the Diluted Alcohol is for no other reason than to aid complete precipitation and removal of the by-product, potassium bitartrate, we can readily understand why the U. S. P. directs to heat the filtrate on the water-bath until all of the alcohol is evaporated, for after the alcohol has accomplished the purpose for which it was used, before filtration, it is of course not wanted in the finished product, the latter being an aqueous preparation. The loss in weight, resulting from the evaporation of the alcohol, however, must be replaced by water, otherwise the finished product will be more concentrated and contain more HI than the formula calls for—that is, the ingredients are used in such proportions as to produce just enough HI to form a thousand Gm. of an approximately ten per cent aqueous solution.

Hydrogen Iodide is not a very stable compound, for it is a comparatively strong reducing agent and is, therefore, readily oxidized even by the oxygen from the air to free iodine and water according to the following equation: $4HI + O_2 = 2H_2O\ 2I_2$—the Iodine changing from the valence of -1 in HI to neutral in elemental iodine while the valence of oxygen is changed from neutral in its elemental state to -2 in water. To prevent, or at least retard, such decompositon a preservative must be used and 20 cc. of hypophosphorous acid are employed for that purpose. The hypophosphorous acid prevents, in a measure at least, the oxidation of the HI to free iodine, because it is a stronger reducing agent, comparatively, than HI, and therefore if any oxidation is to take place it will be oxidized first, and the HI will not be affected until all of the phosphorus in the hypophosphorous acid is oxidized. This is explained by the fact that the phosphorus in the hypophosphorous acid exists in a $+1$ valence and in this state phosphorous is very unstable tending to oxidize to a $+3$ or $+5$ valence which are the more stable forms of phosphorous. This tendency of phosphorus to change from a $+1$ to a $+5$ valence is much greater than the tendency of the -1 iodine is to change to neutral elemental iodine. It is also said that the storing of the Diluted Hydriodic Acid in light-colored bottles in diffused light will retard the oxidation of the hypophosphorous

acid and the hydrogen iodide (light being a reducing agent) and the preparation will keep for six months under those conditions.

In the U. S. P. IX Hypophosphorous Acid in substance was not used but 10 Gm. of potassium hypophosphite were dissolved together with the potassium iodide in water and then mixed with the tartaric acid. Here again double decomposition took place between the potassium hypophosphite and tartaric acid or hydrogen tartrate, producing hypophosphorous acid or hydrogen hypophosphite and potassium bitartrate as a by-product which was precipitated and removed by filtration. In this process, of course, more tartaric acid had to be used for it had to serve the purpose of furnishing hydrogen ions to form HI with the iodide from the KI and also hydrogen ions to combine with the hypophosphite radical from the potassium hypophosphite to form hypophosphorous acid. This latter reaction is obviated by the use of hypophosphorous acid in substance and therefore the U. S. P. X formula directs the use of 122 Gm. of tartaric acid instead of 136.5 Gm. as was directed in the U. S. P. IX.

The Diluted Hydriodic Acid, as all other iodides, is used internally as an alternative in 0.5 cc. doses and it also enters into the preparation of the U. S. P. Syrup of Hydriodic Acid. The liberation of free iodine, therefore, renders the preparation unfit for use, for iodine is very irritant and, if taken internally, would produce its irritant effect on the gastro-intestinal tract. It is for this reason that the U. S. P. states that this preparation should not be dispensed if any free iodine is present. It also gives a test for the detection of free iodine by adding a few drops of Starch Test Solution to 5 cc. of the acid producing a blue-black coloration of starch iodide; formed if free iodine is present. The test, of course, must be negative and show absence of iodine in order to conform to the U. S. P. standards. Since the liberation of free iodine is objectionable, for the reasons already explained, it necessarily follows that Diluted Hydriodic Acid is incompatible with oxidizing agents such as nitrates, permanganates, chlorates as well as ferric, cupric and mercury salts, all of which are capable of liberating free Iodine from hydrogen iodide changing the valence of the Iodine from -1 to neutral while they are reduced to a lower valence such as ferric to ferrous, cupric to cuprous, etc.

The Assay Process is not discussed in the laboratory at the present time, for as I pointed out before, this preparation is manufactured by the freshmen students who have no knowledge of assay processes—Assaying being one of the subjects taught in the second year. But as far as the manufacturing of the preparation is concerned, the students are thoroughly informed at this time, so that they can understand and explain why the particular ingredients were selected, what chemical reactions took place in its manufacture, and why the preparation was put together in the directed order. A knowledge of this kind not only makes the exercise more interesting by having the students understand every detail of the process, but also creates in the operators a confidence in the product which they manufacture—a knowledge which is essential to intelligently practice the profession of Pharmacy and one which is symbolic of an educated pharmacist.

Send in your ballot on the Headquarters site, if you have not done so—your vote evidences your interest.