the drug. It seems to me rather reprehensible to use fluidextract of digitalis in preparing a tincture.

Dr. Arny: Ten years ago if we had heard Professor Scoville make that statement in regard to tinctures, I would have been ready to fight him. Dr. Hatcher in his little book on Materia Medica, published ten years ago, stated that the infusion of digitalis from the fluidextract was scarcely short of criminal, and he got up at the meeting of the New York Branch and stated that the physiological tests now showed that the two were identical. That being the case, I think we must revise our Pharmacopoeia as well as our Materia Medica.

Dr. Wulling: This discussion merely emphasizes the fact that we are not sufficiently qualified to determine the value of the drug unless we test it in more than one way, and the physiological test of drugs has compelled many of us to change our views.

THE ESTIMATION OF MORPHINE IN PILLS AND TABLETS.

H. W. JONES.

The author reviews various methods proposed for extracting morphine with immiscible solvents. The method of estimation described depends on the conversion of morphine into diacetyl morphine and elimination of the diluents employed in making pills and tablets.

The assay of pills and tablets containing morphine or its salts presents certain difficulties because of the comparatively slight solubility of the alkaloid in any of the immiscible solvents ordinarily used. Of the simple solvents, amyl alcohol is the only one which dissolves morphine to any extent and this to so small a degree as to preclude its use where accurate results are desired. In case the morphine is present as a salt, it is always possible to estimate the acid radical but in the case of the sulphate at least, it has been the writer's experience that this procedure leads to high results.

Various compound solvents have been suggested, among which may be mentioned phenylethyl alcohol-benzol, methyl alchohol-benzol, methyl alchohol-chloroform, ethyl alcohol-chloroform and isobutyl alcohol-chloroform, all of which have been used with varying degrees of success. It is not the purpose of this paper to discuss the merits of these different solvents further than to mention that a mixture of one part alcohol and two parts chloroform by volume, as suggested by Williams[1], has been used in this laboratory for the extraction of morphine with excellent results. We have modified slightly the method as described by Williams, using sodium bicarbonate instead of ammonia to liberate the alkaloid. By introducing this modification we have been able to obtain more concordant results, verifying the findings of Puckner..[2]

The object of this paper is to describe a method devised by me and which in my hands has given very good results. The principle of this method is the conversion of the morphine into an acetyl derivative, extraction with chloroform, and subsequent titration with standard acid. As morphine is most commonly used as the sulphate, this salt was used in the investigation. It was

* Presented in Scientific Section A. Ph. A., San Francisco meeting.

[1] A paper presented at the meeting of the American Chemical Society, Washington, D. C., December, 1911. See American Journal Pharmacy, 86, 308.

[2] Journal American Chemical Society, 23 (1901), 470.

first necessary to determine the purity of the sample used, which was done as follows:

One gm. morphine sulphate treated with $BaCl_2$ yielded 0.3129 gm. $BaSO_4$ equivalent to 1.016 gm. morphine sulphate or 101.6 percent; 0.2 gm. morphine sulphate dissolved in water, made alkaline with $NaHCO_3$ and extracted with 5 portions of alcohol-chloroform (1:2). After removing the solvent the residue consumed 5.31 cc. N/10 H_2SO_4 equivalent to 0.19989 gm. morphine sulphate or 99.99 percent. In order to determine if codeine was present in appreciable amounts, 1 gm. of the morphine sulphate was dissolved in water made alkaline with KOH, and extracted three times with chloroform. The chloroform, after filtering through MgO to remove traces of alkali, was distilled off and the residue on titrating consumed 0.25 cc. N/10 H_2SO_4 equivalent in 0.975 percent codeine sulphate. For the purpose of this investigation, the sample was therefore considered as 100 percent pure.

Not to burden the paper with a description of the various experiments made, suffice it to say that the following procedure was finally hit upon: 0.2 gm. morphine sulphate was placed in a clean, dry 120 cc. Erlenmeyer together with 0.1 gm. anhydrous sodium acetate and 3 cc. acetic anhydride. The flask was then fitted with a condensing tube and heated on a steam bath for one hour. The mixture was diluted with 25 cc. of water and the flask rotated until complete solution was effected. The liquid was then transferred to a separator, made slightly alkaline to litmus with ammonia, and extracted with 4 portions of chloroform, after which the chloroform was distilled from the combined extracts, the residue dissolved in 6 cc. N/10 H_2SO_4 and the excess acid titrated with N/100 KOH using cochineal as indicator. By this method the following results were obtained:

1. 5.3 cc. N/10 H_2SO_4 consumed=0.1995 gm. Morphine Sulphate=99.7 percent.
2. 5.32 cc. N/10 H_2SO_4 consumed=0.2 gm. Morphine Sulphate=100 percent.

It will be understood that, although titrating acetyl morphine the factor to be used is that for morphine sulphate, i. e.,—

1 cc. N/10 Acid=.03764 gm. morphine sulphate.

As a further check on the accuracy of the method, a sample of morphine alkaloid, found by titration to be 100 percent pure, was treated in the same manner with the following results:

1. 0.15 gm. morphine taken required 4.99 cc. N/10 H_2SO_4=0.1497 gm. morphine=99.8 percent.
2. 0.15 gm. morphine taken required 4.97 cc. N/10 H_2SO_4=0.1491 gm. morphine=99.4 percent.

Having established in this manner that the conversion of the morphine into the acetyl derivative is quantitative, the method was then tried out on a number of pills and tablets to determine if it was applicable in a practical way. Here a new difficulty arose. Pills and tablets as a rule, contain considerable quantities of starch or milk sugar or both of these substances, and the action of acetic anhydride upon them produces acetyl starch or acetyl lactose, which compounds are soluble in chloroform and if carried through with the acetyl morphine, will obscure the end-point so that the titration becomes unreliable. To obviate this difficulty the following procedure was adopted.

Place a number of pills or tablets equivalent to 3 grains of morphine sulphate in a clean dry 120 cc. Erlenmeyer flask, add 0.1 gm. anhydrous sodium acetate and 4 cc. acetic anhydride. Fit the flask with a condensing tube and heat for one hour on a steam bath. (In the case of pills, coated or uncoated, it is usually necessary, after heating 10 or 15 minutes, to remove the condensing tube and with a stirring-rod disintegrate the pills, afterwards rinsing off the tip of the rod with a few drops of acetic anhydride and then continuing the heating for the balance of the hour.) Dilute the liquid in the flask with 25 cc. of water and rotate until solution seems to be effected. The acetyl compounds of starch or milk sugar being insoluble, will settle on the sides of the flask. Pour the solution into a separator and rinse the flask with two small portions of water, then with two portions of 15 cc. each of chloroform, and finally with two more portions of water, adding all these rinsing to the separator. (It is necessary to rinse the flask with chloroform in order to remove the acetyl starch or acetyl lactose which may hold some of the acetyl morphine.) Place a piece of litmus in the separator and add ammonia water until the liquid is slightly alkaline. Then shake for two minutes and when the liquids have separated, draw off the chloroform through a pledget of cotton into another separator. Repeat the extraction with choloroform three more times, drawing the chloroform extracts into the second separator. Then extract the combined chloroformic liquids with first, 20 cc 10 percent H_2SO_4; second, 10 cc. 10 percent H_2SO_4 and 10 cc. water, and finally with 5 cc. 10 percent H_2SO_4 and 15 cc. water. Combine the aqueous extracts in another separator, make slightly alkaline with ammonia, and extract four times with chloroform. Draw the chloroformic extracts into a flask and distill off the chloroform on a steam bath. Dissolve the residue in 6 cc. N/10 H_2SO_4 and titrate the excess of acid with N/100 KOH using cochineal as indicator.

Below are given some of the results obtained by applying this method to pills and tablets of morphine sulphate:

Pill or Tablet.	Grains Morphine Sulph. by Acetylization.	Grains Morphine Sulph. by Alcohol-Chloroform.
G. C. Pill ¼ gr.	0.239	0.24
G. C. Pill ¼ gr.	0.241	0.246
G. C. Pill ½ gr.	0.498	0.49
G. C. Pill ½ gr.	0.397	0.4
T. T. ¼ gr.	0.237	0.24
H. T. ½ gr.	0.511	0.519
H. T. ¼ gr.	0.231	0.237
H. V. T. 1 gr.	0.985	0.983

It will be seen that the method gives accurate results, and while it offers no particular advantages over the direct-extraction methods, I have found it useful as an alternative when a check assay is desired. A determination may be run in about two hours, and no troublesome emulsions are experienced. On the other hand, its field is limited, as it can be applied only to dry mixtures. The presence of moisture would of course inhibit the acetylization process.

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