SECTION ON PRACTICAL PHARMACY AND DISPENSING, AMERICAN PHARMACEUTICAL ASSOCIATION

DIACETYLMORPHINE U. S. P. AND ITS HYDROCHLORIDE.*

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Two alkaloidal preparations newly admitted to the Ninth Revision of the Pharmacopoeia are diacetylmorphine alkaloid and its hydrochloride. Undoubtedly both will receive considerable attention from the pharmacist and chemist because of their being newly admitted to the Pharmacopoeia and because of the rather variable composition and behavior of those samples found upon the market. In the following paper I have endeavored not only to point out some of these variations but also to cite the results of a number of experiments, etc., made upon these two products.

Much has been written and said about the melting point of diacetylmorphine alkaloid and especially of diacetylmorphine hydrochloride. The Pharmacopoeia states that the alkaloid melts between 171.5° and 173.5° C. Four samples of this product made by different manufacturers and obtained in the open market were tested and found to melt sharply and distinctly at 172° C. Therefore, it would seem that the official specification, that it shall melt between 171.5° and 173.5° C. is quite liberal.

The determination of the melting point of the hydrochloride, however, offers a number of difficulties. The Pharmacopoeia states that it "melts at about 230° C. with decomposition." This means much or little. I have found it difficult to obtain any definite melting point with this salt, due to the fact that it slowly decomposes when subjected to temperatures above 200° C. In order to show the variations which occur in determining this melting point the following experiments were made, all upon portions of the same sample of diacetylmorphine hydrochloride:

Experiment A. A melting point determination was made in the ordinary way in such a manner, however, that the rise in temperature was at the rate of $4^1/_2$° C. during each minute of heating. The salt began to acquire a darker color at 190° C., first yellow then brown, and melted at 225° C. The total time of heating amounted to almost forty-five minutes.

Experiment B. Upon another portion of the same sample of diacetylmorphine hydrochloride, a melting point determination was made, in such a way, however, that the rise in temperature progressed at the rate of 6.5° C. during each minute of heating. The substance began to darken at about 200° C. and melted at 228° C. The total time of heating amounted to about thirty minutes.

Experiment C. Upon a third portion of the same sample a melting point determination was made in such a way that the rise in temperature was at the rate of 10° C. for each minute of heating. The substance darkened at 200° C. and melted at 232° C. The total time of heating in this case amounted to about twenty minutes.

* Read before Section on Practical Pharmacy and Dispensing, A. Ph. A., Atlantic City meeting, 1916.

Experiment D. In a similar manner a fourth portion of the same sample was subjected to a melting point determination in such a way, however, that the rise in temperature was at the rate of 20° C. for each minute of heating. The salt began to darken at about 210° C. and melted at 235° C. The total time of heating in this case amounted to ten minutes.

The foregoing four experiments were repeated with another firm's product and gave similar results.

The conclusion drawn from these variations in the melting point is that diacetylmorphine hydrochloride slowly decomposes and liquefies at a temperature which varies according to the length of time during which it is exposed to this temperature. Therefore, a fifth experiment was made upon another portion of the sample of diacetylmorphine hydrochloride strictly in accordance with directions of the Ninth Revision of the Pharmacopoeia, for determining melting points. The method is rather elaborate probably too much so for the average pharmacist. It calls for a stirring device, a standard thermometer, an auxiliary thermometer for emergent stem corrections on the main thermometer, together with other rather complicated directions and calculations. Upon closely following out all these directions, repeated determinations upon portions of the same sample yielded similar results. However, no two samples of different manufacturers gave the same melting point. The four samples varied between 228 and 234° C.

The Pharmacopoeia does not mention any allowable loss in weight upon heating in a drying oven. However, the formula of the alkaloid calls for an anhydrous product, and that of the hydrochloride calls for the presence of one molecule of water which is the equivalent of 4.88 percent. The four samples of diacetylmorphine alkaloid were practically anhydrous. Those of the hydrochloride varied from 3.9 to 4.71 percent loss of weight after carefully drying at 60° C. in an oven.

Ash determinations were made on all samples both alkaloid and hydrochloride. In order to obtain a weighable residue two grammes of each sample were used The results were as follows:

Hydrochloride.		Alkaloid.	
1	0.080 percent residue	1	0.031 percent residue
2	0.042 percent residue	2	0.036 percent residue
3	0.051 percent residue	3	0.063 percent residue
4	0.072 percent residue	4	0.066 percent residue

The Pharmacopoeia specifies that no weighable ash remains on incinerating 0.5 Gm. of the substance. All samples, therefore, would pass their requirement.

All samples both alkaloid and hydrochloride withstood the tests for presence of "other alkaloids" and ammonium salts.

One sample of the hydrochloride turned slightly dark when dissolved in concentrated sulphuric acid, in accordance with the official requirements, thereby showing the presence of small quantities of "readily carbonizable organic impurities."

The results of the tests for presence of morphine varied somewhat with the different samples used. The test in the Pharmacopoeia reads:

> "Dissolve about 0.05 Gm. of the potassium ferricyanide in 10 mils of distilled water, add one drop of ferric chloride T. S. and then 1 mil of an alcoholic solution of Diacetylmorphine (1 in 100); no greenish or blue color is produced at once." Of the four samples of alkaloid and four of hydrochlo-

ride tested, one sample of the hydrochloride turned distinctly greenish at the expiration of about five seconds. It does not seem quite clear whether such a sample would pass the requirement of not turning greenish or blue at once. The other samples withstood the test for periods of time varying from 15 seconds to 2 minutes.

Conclusion: The foregoing comparisons prove that the requirements of the Pharmacopoeia regarding the purity of diacetylmorphine alkaloid and hydrochloride are by no means too severe and will be easily met by the manufacturers. All the samples most commonly found on the market to-day while showing some variations are of sufficient purity to pass the official tests.

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SODIUM CACODYLATE BETTER THAN SALVARSAN.*

It were a good thing if physicians could be made to understand that sodium cacodylate (dimethyl arsenate) will do all that salvarsan and neo-salvarsan can do, while being much safer to handle. However, several years of experience with this remedy, administered intravenously in a wide variety of conditions (and at first, it must be admitted, with many failures), have convinced me that our current dosage is too small. For some time my practice has been never to give less than 10-grain doses, and often even as high as 30 grains, repeating the dose in four days. Those cases that failed to respond to the 10-grain dose have cleared up quickly under the 30-grain dose, and I have never seen any constitutional arsenic symptoms arise from this large dosage.

In treating syphilitic lesions with cacodylates, we should employ mercury either before or conjointly with the cacodylates, otherwise we are likely to produce that spirochete-fixation often produced by the salvarsan preparations, and known as the arsenic-fast condition. In tertiary lesions, iodine should be prescribed in conjunction, inasmuch as iodine is a liberator of encysted spirochetes and the cacodylate an eliminator by way of the lymph and blood streams.

The cacodylates are valuable remedies for many pathologic conditions, including skin diseases, as well as for infections, while the tonic and alterative properties of arsenic are well known.

We should administer more remedies by the intravenous route. The administration of thousands of injections during the course of several years gives me the assurance that this is a rational and safe procedure to follow.

W. N. Fowler.

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**Clinical Medicine*, January 1917.