most of the other morphine salts contain a considerably large amount of other opium alkaloids. These by-alkaloids should be determined also, inasmuch as they are ether-soluble and may seriously interfere with the estimation of morphine in mixtures with other ether-soluble alkaloids such as atropine, etc. This can easily be done by the isobutyl alcohol-chloroform method, as has been shown by one of us a short time ago.—*(Deutsch-Amerikanische Apotheker Zeitung, Jan., 1913.)*

Analytical Laboratory Sharp & Dohme.

THE COMPOSITION AND ASSAY OF HEROIN HYDROCHLORIDE AND DIACETYL-MORPHINE HYDROCHLORIDE.*

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Upon assaying certain preparations containing heroin hydrochloride, it was found that the amount of alkaloid was about 5% less than that supposed to be present, and upon going further into this matter it was shown that the direct assay of heroin hydrochloride, by the same method, gave a similar result. The method of assay was then tested upon the base, heroin, and upon diacetyl-morphine which had been purified by recrystallization and the result of these tests showed that the method was entirely reliable. Heroin hydrochloride is referred to in the literature in all cases which we could discover, as the anhydrous salt of diacetyl-morphine, this being the formula assigned to the product by its manufacturers. A like state of affairs exists in regard to the hydrochloride of diacetyl-morphine, but on the contrary we find that heroin hydrochloride contains 1 molecule of water. Two samples of diacetyl-morphine hydrochloride, obtained from different manufacturers, were found to have the same composition, while another sample from a third source consisted of the anhydrous salt. On account of the close scrutiny to which pharmaceutical products are frequently subjected nowadays it is well to clear up such confusion by careful experiments and to call attention to the existing facts.

Heroin Hydrochloride:—When heroin hydrochloride is heated at 100° there is a decided loss in weight. Quantitative experiments are difficult to carry out owing to the readiness with which the resulting product absorbs moisture from the atmosphere; however, the loss in weight is no more than that resulting from the loss of 1 molecule of water. The substance is not changed in any of its essential characteristics and dissolves completely in water after heating. When the heated product is allowed to stand in the air for a few hours its weight reverts to exactly the original value.

Ten grams of heroin hydrochloride were dissolved in about 150 cc. water and precipitated carefully with diluted ammonia, until a slight excess of the latter had been used. The crystalline precipitate was filtered upon a Büchner funnel, washed free from ammonium chloride and dried. The combined filtrate was shaken out twice with a little chloroform and the latter solution evaporated until the solvent had been completely removed. The crystalline precipitate amounted

* Read at Scientific Section, Detroit.

to 8.4 grams to which is to be added .1 gm. extracted with chloroform. The theoretical amount required for the anhydrous salt is 9.10 gms.

The above experiment was repeated with another sample of heroin hydrochloride which melted at 225-230° (uncor.). From 10 grams there were obtained 8.55 grams of heroin which melted at 169°-170° (uncor.) and .15 grams were extracted with chloroform.

Five grams of heroin melting at 169°-171° (uncor.) were dissolved in dilute hydrochloric acid, just enough acid being used to effect solution, the volume being about 125 cc. The solution was then precipitated carefully with ammonia and the precipitate and extract obtained exactly as from the hydrochloride. The dry precipitate amounted to 4.88 gms. while the extract yielded .1 gm. additional. There had been practically no loss.

1.53 gms. heroin were treated on a watch-glass with about .4 cc. of concentrated hydrochloric acid and stirred quickly. The heroin goes into solution completely and this is soon followed by a separation of the hydrochloride. The product was placed in vacuum to remove water and a slight excess of hydrochloric acid. When dry, it was pulverized and again placed in vacuum until a constant weight had been shown which was 1.77 gms. This is slightly in excess of that required for a hydrochloride containing 1 molecule of water.

Diacetyl-Morphine Hydrochloride:—This substance was prepared by the action of acetic anhydride on morphine and was purified by repeated crystallization from benzol until there was no further change in the melting-point which was 170°-171° (uncor.).

Eight grams of pure diacetyl-morphine were dissolved in a slight excess of dilute hydrochloric acid, and then precipitated with ammonia in the same manner as has already been described under heroin hydrochloride. The dried precipitate amounted to 7.88 grams.

A quantity of pure diacetyl-morphine was dissolved in about seven times its weight of dry benzol and treated with the calculated quantity of a saturated solution of hydrochloric acid in absolute alcohol. After standing one-half hour a large proportion of anhydrous diacetyl-morphine hydrochloride crystallized out. The crystals were filtered upon a Büchner funnel, washed with water-free benzol and dried. They melted at 131°-135°, which is considerably higher than the melting-point of heroin hydrochloride. This product did not show any loss in weight when it was heated at 100°. It lay in the air for several days without change in weight, but when a portion of it was powdered, there was a small increase of weight during the first twenty-four hours, followed by a rapid absorption of water sufficient in amount to correspond to one molecule. Nine grams of this salt were precipitated with ammonia in the usual manner and there were obtained 8.02 grams of precipitate and .11 grams of extract. The theoretical amount required for the anhydrous salt is 8.19 grams.

One and five-tenths grams pure diacetyl-morphine were treated on a watch-glass with a slight excess of 15% hydrochloric acid. The resulting product was freed from water in vacuum, powdered with a glass rod and then again placed in vacuum until a constant weight was obtained. The increase in weight was .2216 grams, while the monohydrated salt requires theoretically an increase of .2220

grams. The salt produced in this manner melts lower than the anhydrous salt and also lower than heroin hydrochloride. 218°-224° (uncor.).

Three samples of commercial diacetyl-morphine hydrochloride obtained from different manufacturers were examined. (1) The sample melted at 230°-238° (uncor.). Ten grams gave 8.91 grams of precipitated alkaloid and .11 grams extracted. 9.02 grams were recovered while the theoretical for the anhydrous salt is 9.10 grams. The product was therefore the anhydrous salt. (2) The sample melted at 224°-228° (uncor.). From 10 grams there were obtained 8.6 grams of precipitate and .12 grams of extract. The product is therefore the monohydrated salt. (3) The sample melted at 225°-230° (uncor.) and showed a decided loss in weight when treated at 100°. It is therefore the monohydrated salt.

Since the completion of these experiments our attention has been called to a statement by Schaefer (*American Journal of Pharmacy*, 82, 220), that only the monohydrated salt can be found on the market. He found that this salt when dehydrated, regains its water quickly from the air, but we have shown that this is not true of the anhydrous salt which separates from solution.

Assay:—Heroin or diacetyl-morphine may be accurately estimated by dissolving in excess of 1/10 normal hydrochloric acid and titrating the excess of acid with 1/50 normal sodium hydroxide using cochineal as an indicator.

	Weighed Sample.	Found.	Found Per Cent.
Pure diacetyl-morphine.....	.1362 grams	.1354	99.42
	.1735 grams	.1725	99.44
Heroin.....	.1323 grams	.1317	99.53
	.1336 grams	.1328	99.41

For the estimation of the alkaloid in its salts the following method is recommended:—An amount of the preparation representing at least one-tenth gram of the alkaloid and contained in 10 cc. of solution is treated with 20 cc. chloroform and sufficient 10 *per cent.* ammonia to render it slightly alkaline. After shaking vigorously, the chloroform is drawn off into a container suitable for titrating. The extraction with chloroform is repeated three times, after which the combined chloroform extract is evaporated. Add 5 cc. of 1/10 normal hydrochloric acid or sufficient to completely dissolve the alkaloidal residue then add a few drops of cochineal solution and titrate the excess of acid with 1/50 normal sodium hydroxide. The results obtained are very close to the theoretical.

Scientific Laboratory of Parke, Davis & Co.

THE GLANDS OF INTERNAL SECRETION AND THEIR IMPORTANCE AS THERAPEUTIC AGENTS.

CAREY PRATT MCCORD.

The animal body, it appears, manufactures its own drugs. These drugs are the derivatives of the glands of internal secretion. These substances elaborated by the secretory cells of these glands are discharged into the circulation and carried to the various parts of the body. There they react upon the tissues in a manner for the well-being of the body as a whole.