

## Scientific Section

Papers Presented at the Sixty-Second Annual Convention

### MORPHINE NITRATE AND MORPHINE ACETATE.\*

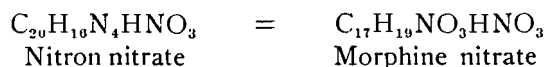
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The variation in purity of commercial morphine nitrate and morphine acetate is very marked, as we have found in our experiments on numerous samples of the salts. In order to find out the extent of such variations the following experiments were undertaken with five samples of the salts, manufactured by different firms and purchased on the open market. The samples were marked I-II-III-IV-V and the methods applied for estimating the purity were the following:

*I. Process similar to the U. S. P. method for estimating morphine in opium:*—.85 gm. of the morphine salt is dissolved in 15cc. of water, and the solution is mixed with 7.5cc. of alcohol, 15cc. of ether and 2.2cc. of ammonia water. The mixture is then shaken for ten minutes and allowed to stand over night. The crystallized morphine is collected on a filter, washed with etherized water and dried at 60° to constant weight.

*II. Puckner's Method:*—(*Journ. Amer. Med. Assn., Sept. 13, 1913*)—.5 gm. of the morphine salt is dissolved in 20cc. of water and mixed with 0.25cc. of ammonia water, the mixture is shaken for five minutes and allowed to stand over night. The morphine is collected on a filter, washed with morphinated water, dried at 60° to a constant weight. To the amount of morphine found .0076 gms. is added, the amount of morphine soluble in the aqueous liquid.

*III. Nitron Method:*—.35 gms. of the morphine salt is dissolved in 50cc. of water and mixed with about 5cc. of a 10 per cent. solution of nitron in 5 per cent. acetic acid. After allowing the mixture to stand in a refrigerator for two to three hours it is filtered through a Gooch crucible and the precipitate is washed with ice water (using not more than 10cc. of the latter) and dried to constant weight. The weight multiplied by .93 gives the amount of morphine nitrate, according to the equation:—



*IV. Schäfer Method:*—(*Amer. Journ. Pharm., 1913, page 439.*)—.85 gm. of the morphine salt is finely triturated in a small mortar with a sufficient quantity of purified sand and an excess of sodium bicarbonate. The mass is moistened with a little water and allowed to dry again at a temperature not exceeding 30° to 40°. The mixture is then transferred to an Erlenmeyer flask, and to the con-

\* Scientific Section at Detroit.

tents of the flask a freshly prepared mixture, consisting of one volume of methyl alcohol and four volumes of chloroform is added, and the mortar is carefully rinsed with the same liquid. The mixture is allowed to stand for one hour with moderate but frequent shaking. The liquid is then filtered through a small filter and the residue washed thoroughly with three to four portions of about 10cc. each of the above solvent. The combined filtrate and wash-liquids are distilled off, the residue taken up with an excess of N/20 sulphuric acid and the excess of the acid titrated in the usual way using cochineal or methyl red as indicator.

*V. a. Isobutyl alcohol-chloroform method.*—.5 gm. of the morphine salt is dissolved in 20cc. of water, the mixture made alkaline with sodium bicarbonate and shaken out with 50cc. of a mixture of equal parts of isobutyl alcohol-chloroform. The chloroformic solution is drawn into another separator and the aqueous solution shaken out twice more with each 30cc. of the above chloroform-isobutyl alcohol mixture. The combined alcohol-chloroform solutions are shaken out once with water in order to remove any suspended alkali and are then shaken out with 20cc. of tenth-normal sulphuric acid, followed by two portions of 20cc. each of water. The combined aqueous solutions are then titrated with standardized alkali in the usual way.

*V. b.* As an alternative process .05 gm. of the morphine salt was dissolved in 20cc. of water, the aqueous solution made faintly alkaline with ammonia and then shaken out as just given with various portions of a mixture of isobutyl alcohol-chloroform. The combined alcohol-chloroform solutions were then evaporated in a vacuum and the residue titrated in the usual way.

*VI. Vanderkleed Method:*—(*Journ. Amer. Pharm. Assn.*, Aug., 1913.)—A solution of the morphine salt equivalent to about .2 gm. of morphine is dissolved in 15 cc. of water in a separator, the solution mixed with amyl alcohol, made alkaline with the ammonia water and heated on a steam-bath at 80° for about five minutes. The mixture is then shaken for about two minutes and, after allowing to cool, the aqueous layer is drawn off into a second separator and the amyl alcohol transferred into a 300 cc. Erlenmeyer flask. The aqueous solution is extracted twice more with amyl alcohol in the same way. The combined amyl-alcoholic solutions are evaporated in an oil-bath to dryness. (We have found evaporating solution in a vacuum gives better results.) The residue is dissolved in 20 cc. of N/20 sulphuric acid and the excess of acid is titrated back with N/20 potassium hydroxide solution, using methyl red as indicator.

*VII. Buchbinder Method:*—3 gm. of the morphine salt is dissolved in 30 cc. of lime water; to the solution .5 gm. of ammonia chloride is added and 30 cc. of a mixture consisting of two parts of chloroform and one part of alcohol by volume. After shaking the mixture well, the chloroform-alcohol solution is drawn off into another separator and the aqueous solution shaken out with various portions of the chloroform until the latter no longer takes up morphine. (We have found that even by extracting the aqueous solution ten times with chloroform not all the morphine is removed, but that only about three shakings are necessary, when chloroform containing about 10 per cent. of alcohol is used for the extraction.) The combined chloroform-alcohol solutions are evaporated to dryness, the residue is dissolved in 10 cc. of neutral alcohol and a convenient excess of N/50 sul-

phuric acid is added. The alcohol is then evaporated and the acid solution titrated with N/50 potassium hydroxide, using either cochineal or methyl red as indicator. The results given below were obtained by using a chloroform-alcohol mixture throughout.

In order to determine the accuracy of these methods we applied them to pure morphine, which had been obtained by recrystallizing the alkaloid several times from the alcohol. When titrated the alkaloid showed a purity of 100.0 *per cent.* and 99.7 *per cent.*

The results obtained with pure morphine, the samples of morphine nitrate and morphine acetate are given in the following table:—

PURE MORPHINE								
U. S. P. Process	Puckner Method	Nitron Method	Schafer Method	Isobutyl alcohol-chloroform Method	Amyl alcohol Method	Modified Buch-binder Method		
	96.6%		100.3%	98.2%	98.6%	98.7%		
	97.6		102.5			98.2		
MORPHINE NITRATE.								
I.	85.9%	87.9	87.1	97.4	84.8	88.04*	86.4*	83.5
				95.7				
II.	88.0	86.5	87.2	90.8	82.9	88.5*	85.2*	86.6
				93.6				
III.	90.7	88.7	90.9	92.2	88.0	86.8*	83.4*	86.7
				92.2				
IV.	87.8	89.9	89.6	92.6	89.7	84.7*	86.3*	86.4
				93.2				
V.	87.0	88.5	89.3	90.8	87.5	85.8*	84.2*	86.3
				94.5				
MORPHINE ACETATE.								
I.	95.46	93.5		121	99.8		101.3*	96.8
II.	90.63	86.8		108	97.8		98.1*	92.2
III.	92.19	93.5		112	93.8		97.7*	93.8
IV.	93.08	92.6		113	93.8		97.2*	95.7
V.	91.41	88.0		117	97.0		98.4*	94.3

\* These results were obtained by evaporating the solutions of the morphine in the immiscible solution to dryness in a vacuum.

From these experiments it is evident that the purity of morphine nitrate rarely is above 90 *per cent.* and that the purity of morphine acetate is also far below 100 *per cent.* The latter is the more surprising as every sample exhibited a strong odor of acetic acid. If there is a loss of acetic acid, the percentage of morphine in the sample should be above 100 *per cent.*, provided the sample originally showed this purity.

In view of these facts it would be advisable for the Sub-Committee on Organic Chemicals of the Revision Committee of the U. S. P. to take this matter up, give requirements for a certain purity of these salts and furnish at the same time a reliable assay process.

By all the methods given in this paper the total alkaloids present in the morphine salts are determined. It is a well-known fact, that morphine sulphate and

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.)

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### 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

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\* Read at Scientific Section, Detroit.