AN IMMISCIBLE SOLVENT METHOD FOR THE DETERMINATION OF MORPHINE IN OPIUM.

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During the past few years, a number of American and European chemists have suggested various methods for the determination of morphine in opium. The general opinion is that a desirable method should not involve the use of aliquot parts, and the morphine should be extracted with an immiscible solvent. The objection to the use of immiscible solvents is that owing to the insoluble nature of morphine in the solvents so far suggested, it has not been practicable to use more than about 1 Gm. of opium. Most American chemists consider that not less than 4 Gm. of opium should be used for the assay because of the lower experimental error.

After conducting a considerable number of experiments, we have finally developed a method which may prove reasonably satisfactory. The method is somewhat similar to an unpublished method by Eder and Wackerlin (1) with the exception that a different solvent is used and 4 Gm. of opium are taken for the assay. The solvent is a neutral mixture of 60 volumes of chloroform and 40 volumes of benzyl alcohol; 100 cc. of the mixture under the conditions of the assay will extract over 1 Gm. of morphine alkaloid. The details of the method are as follows:

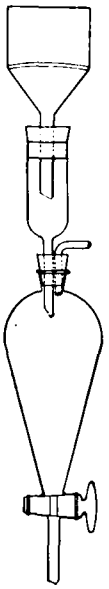

Fig. 1.

Place 4 Gm. of opium which may be in the form of gum, powder or granules, in a 100-cc. porcelain mortar with a rough inner surface, add 8 to 12 cc. of distilled water and triturate with a rough pestle until a smooth paste is formed, free from discernible particles. This operation requires about 10 to 15 minutes. Add 2 Gm. of calcium hydroxide, 2 cc. of distilled water and continue triturating for about 5 minutes. A rubber policeman with one end sealed, should be used to scrape particles from pestle and sides of mortar during trituration. Then add three 10-cc. portions of distilled water, triturating for about 2 minutes, after each addition. Stir the mixture frequently during 10 minutes, then add 1 Gm. of wood flour,[1] which facilitates filtration. Mix well and allow to stand 5 minutes, stirring frequently.

Thorough trituration of the opium, even when in the form of powder is of great importance. Even with powder, low results are possible if the opium is merely shaken with the prescribed amount of water for 30 minutes and then with calcium hydroxide for 30 minutes before filtering.

The filtering apparatus consists of a short wide form 17G3, Jena fritted glass Büchner type filter funnel with a disc 65 mm. in diameter. The funnel is connected by means of a 32-mm. carbon filter tube to a 500-cc. separator, which is connected to a vacuum pump. The figure shows arrangement of the apparatus.

Before starting the filtration, place about 2 cc. of benzyl alcohol in the separator to prevent foaming during filtration. The mixture in the mortar is transferred to the filter, as much as possible of the residue left in the mortar being removed by means of the policeman. Suction is applied until all of the liquid has drained into the separator. The vacuum is broken and the mortar and pestle washed twice with two 8 cc. of lime water, using the policeman to remove particles. The combined washes are mixed thoroughly in the funnel with the residue for about 2 minutes by means of the policeman, a thin glass rod with one end drawn to a dull point may

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[1] The wood flour was obtained from Eimer & Amend, New York, N. Y.

be used to detach cake from the corner of the funnel. Suction is again applied until the liquid has drained into the separator. The mortar is then rinsed three times with 15 cc. of lime water. As before, each wash is thoroughly mixed with the residue in the funnel before applying suction.

The 5 washes are sufficient to remove all soluble and insoluble matter from the mortar and pestle. The residue in the funnel is now washed four times with 15 cc. of lime water each time. The suction is discontinued while each wash is thoroughly mixed with the residue. The filtrate may be slightly cloudy. The carbon filter tube and the inside of the lower portion of the funnel are rinsed with 5 cc. of distilled water. To the filtrate in the separator, add 75 cc. of solvent which is a neutral mixture of 60 volumes of chloroform and 40 volumes of benzyl alcohol.[1] Add 3 Gm. of ammonium chloride and shake vigorously for 2 minutes. Allow to separate for about 15 minutes. The solvent and the small quantity of emulsion is filtered through a small plug of absorbent cotton in a 32-mm. carbon filter tube into a 250-cc. separator. The last portion of the solvent is blown out by applying the mouth to end of filter tube. Wash the plug of absorbent cotton once with 5 cc. of solvent. Add 5 cc. of solvent to the alkaline liquid, shake gently for a few seconds. After about one minute, transfer solvent to the filter tube and repeat once. The solvent is blown out of the filter tube as before. The solvent in the 250-cc. separator is drawn into another 250-cc. separator, the small quantity of alkaline liquid is transferred to the 500-cc. separator containing the bulk.

Place 20 cc. of solvent in the empty 250-cc. separator, shake a few times, transfer to the 500-cc. separator, shake vigorously for 2 minutes, separate and repeat the routine twice. In all, the alkaline opium solution is extracted 4 times, once with 75 cc. and 3 times with 20 cc. of solvent. The solvent from each shake is filtered through the same plug of absorbent cotton that was used for the first shake. The solvent containing the alkaloids in the 250-cc. separator is now shaken for one and one-half minutes with a mixture of 3 cc. $N/1$ sodium hydroxide and 9 cc. of water, and allowed to separate for 20 minutes. The solvent is transferred to another 250-cc. separator, leaving the alkaline solution and any emulsion in the first separator. The solvent is shaken for one and one half minutes with 10 cc. of $N/10$ sodium hydroxide, allowed to separate and the solvent transferred to a third 250-cc. separator. The alkaline solution is added to the first alkaline extract in the first separator. 10 cc. $N/10$ sodium hydroxide is added to the empty second separator. After shaking a few times, the solution is added to the solvent in the third separator. The mixture is shaken for one and one-half minutes and the above routine repeated. The solvent is given two more shakes with 10 cc. of $N/10$ sodium hydroxide. In all, the solvent is shaken out 5 times, the last 4 times with 10 cc. $N/10$ sodium hydroxide. The sodium hydroxide solution of morphine is now shaken with 5 cc. of chloroform for a few seconds. The separated chloroform and the small quantity of emulsion is filtered through a fresh plug of absorbent cotton in a 32-mm. carbon filter tube and blown out. A second shake with 5 cc. of chloroform follows. The plug of absorbent cotton is then washed twice with a few cc. of distilled water; the chloroform is separated and the aqueous portion added to the sodium hydroxide solution of morphine, which is transferred to a tared 125-cc. Erlenmeyer flask and a few drops of methyl red indicator added. The chloroform is shaken with 5 cc. of distilled water and separated; the water is used to rinse out the separator which contained the sodium hydroxide solution of morphine. The separator is then rinsed out twice, each time with 5 cc. of $N/1$ sulfuric acid. Each wash is passed through the cotton plug in the filter tube, the filtrate passing into the Erlenmeyer flask containing the morphine solution.

The separator is again rinsed out with two 5-cc. portions of distilled water and the same routine followed. Sufficient $N/1$ sulfuric acid is then added to give a distinct acid reaction, usually 1 to 3 cc. will be required. If the solution is too dark to see the change in color, add a small piece of blue litmus paper. The flask containing the acidified solution is heated on a steam-bath with frequent shaking until the globule of chloroform has disappeared, the flask is then immersed in a steam-bath up to the neck and a stream of compressed air passed over the liquid until the solution weighs about 30 Gm. The solution is cooled, neutralized with 10% ammonia solution (about 1 drop will be required) and sufficient distilled water added to bring the weight up to 34 Gm. Add 2 cc. alcohol, 15 cc. ether, 0.6 cc. 10% ammonia solution and 0.5 Gm. ammonium

[1] Sufficient solvent for the assay is first shaken with 50 cc. of distilled water and sufficient ammonia to neutralize free acid.

sulfate, stopper the flask tightly and agitate without wetting the stopper until the morphine separates. Allow to stand over night at room temperature. The addition of ammonium sulfate induces rapid precipitation.

Remove the stopper and brush any adhering crystals back into the flask. Decant the ether layer through a 9-cm. filter paper and wash paper with 5 cc. of ether. Rinse the flask and contents with 15 cc. of ether. Pass the ether wash through the filter and again wash the filter with 5 cc. of ether. If necessary, wash the funnel tip with a few cc. of ether.

Pour the aqueous layer upon the filter without trying to remove all of the crystals from the flask. Wash the crystals in the flask and the contents of the filter with morphine-saturated water. Seven washes are given—5 cc. each time. Wash the crystals into the cone of filter with a few cc. of morphine-saturated water dropped from a pipette, followed by 2 cc. of distilled water. Place 5 cc. of methanol in the flask. Rotate the flask to detach the crystals from the sides and neck. Heat to the boiling point. Agitate to dissolve as much of the morphine as possible and pour the hot solution over the morphine on the filter, receiving the filtrate in a suitable flask. Repeat this treatment 13 times, using 5 cc. of methanol each time. A total of 70 cc. of methanol is used.

After the second or third wash, break up any clumps of alkaloid on the filter with a glass rod. After all visible morphine has been dissolved from the flask and filter, open the filter flap and drip the hot methanol over the edge of filter and on any morphine held in the flap. After the prescribed number of washes have been given, drip 5 cc. of cold methanol from a pipette on the outside tip of funnel to dissolve traces of morphine which may crystallize out from the methanol.

Cool the filtrate, add exactly 25 cc. of $N/10$ sulfuric acid and evaporate on a steam-bath to about 25 cc. Cool the liquid, dilute with 25 cc. of distilled water and titrate the excess acid with $N/10$ sodium hydroxide, using methyl red as the indicator. Each cc. of $N/10$ acid is equivalent to 0.02852 Gm. of anhydrous morphine alkaloid.

To 75 cc. of methanol, add 25 cc. of $N/10$ sulfuric acid. Evaporate on a steam-bath to about 25 cc. and titrate the excess acid with $N/10$ sodium hydroxide.

A correction for the acidity or alkalinity of the methanol is applied to the results obtained after titrating the morphine solution. The morphine obtained by this method is free from non-phenolic alkaloids. We have found that the morphine obtained by the U. S. P. XI method contains about 4% of non-phenolic alkaloids. Wallingford and Homeyer (2) have shown, that in addition to the non-phenolic alkaloids in the U. S. P. X assay morphine, there are other water-soluble basic substances, probably phenolic in character. So far, it has not been found practicable to remove these phenolic basic substances except by reprecipitation from water.

As the result of a few experiments, we have found that loss of morphine in the assay is to some extent counter-balanced by these water-soluble basic substances. Of course, with opium from various sources, these impurities will vary in quantity.

The following is a comparison of the results obtained by the U. S. P. XI and the new method. Powdered opium was used.

	Morphine Alkaloid by U. S. P. XI Method.	Temperature during Precipitation.
Chemist A	11.27%	22.8°
	11.25	to
Chemist B	11.25	25° C.
	11.36	
Average	11.28%	

	Morphine Alkaloid by New Method.	Temperature during Precipitation.
Chemist A	11.59%	23° to 26.5° C.
	11.63	23° to 25.5° C.
	11.68	19° to 25.5° C.
	11.68	17° to 27.0° C.
Chemist B	11.68	19° to 26.0° C.
Average	11.65%	

The morphine obtained by the U. S. P. XI method contains about 4% of non-phenolic alkaloids. If this correction is applied the results are as follows:

U. S. P. XI after Correcting for Non-phenolic Alkaloids.	New Method Free from Non-phenolic Alkaloids.
Morphine alkaloid	Morphine alkaloid
10.83%	11.65%

The following results were obtained with one sample of opium:

Morphine Alkaloid by U. S. P. XI Method.	Temperature during Precipitation.	Morphine Alkaloid by New Method.	Temperature during Precipitation.
13.59%	17° to 26° C.	14.19%	17° to 26° C.
Corrected for non-phenolic alkaloids			
13.05%	....	....	....

The results obtained by the new method were 0.38% to 0.6% higher than by the U. S. P. XI method. After correcting for the non-phenolic alkaloids the difference is 0.82% to 1.14%.

In all assays by the U. S. P. XI and the new method, the volume of methanol used was 75 cc.

REFERENCES.

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BROMOALKYL DERIVATIVES OF SALICYLIC ACID.*

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An unsaturated alkyl chain containing bromine has frequently been found of considerable value in producing a sedative effect in barbituric acid derivatives. Pernocton, for example, is secondary-butyl-β-bromoallyl barbituric acid. A combination of the sedative bromoalkyl group with the antipyretic and analgesic salicylic acid grouping offered interesting possibilities. We therefore prepared bromoallyl salicylate (I), and its acetyl derivative (II). The former was made by condensing sodium salicylate with 2,3-dibromopropene, and the latter by acetylating the condensation product. Biological tests revealed that both compounds were somewhat superior to acetyl salicylic acid in antipyretic activity, but were almost three times as toxic. The advantage of enhanced antipyretic action was therefore outweighed by increased toxicity.

Having in mind the preparation of α-bromoacrylyl salicylic acid we made three attempts at the preparation of intermediates:

(1) α-bromoacrylyl chloride from potassium α-bomoacrylate and thionyl chloride.

(2) α-bromoacrylyl chloride from potassium α-bromoacrylate and phosphorus oxychloride

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