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THE ASSAY OF
PREPARATIONS CONTAINING PILOCARPINE
AND THE CHARACTERS OF
PILOCARPINE NITRATE AND HYDROCHLORIDE.

BY
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The Assay of Preparations containing Pilocarpine and the Characters of Pilocarpine Nitrate and Hydrochloride.*

By H. A. D. JOWETT, D.Sc.

Our knowledge of the alkaloids of jaborandi is in a very unsatisfactory condition, especially that relating to the assay of preparations containing pilocarpine and to the characters of the two salts used in medicine, viz., the nitrate and hydrochloride.

As regards the assay, it is possible to determine the amount of total alkaloid contained in the leaves or their preparations with a fair degree of accuracy. This information, however, is of little value, for it gives us no indication of the amount of pilocarpine contained in the total alkaloid, and it must be assumed that on the pilocarpine alone depends the therapeutic value of the preparation.

The nitrate and hydrochloride are somewhat largely used in medicine, but the official characters of these salts as given in the various Pharmacopœias are very unsatisfactory and hardly serve to identify the alkaloid, much less to determine its purity. The only salt of pilocarpine officially recognised by the B.P. is the nitrate, of which the following description is given :—

“A white crystalline powder, soluble in 8 to 9 parts of cold water, slightly soluble in cold, freely soluble in hot alcohol (90 per cent.).”

In commerce the salt generally occurs in distinct crystals and can always be obtained in this form. A little more definite information should be given as to its solubility, the factors above mentioned for water being incorrect. The test for identity which is given can hardly be considered distinctive, and depends on the oxi-

* Read before the British Pharmaceutical Conference at Plymouth, July, 1899, and reprinted from the *Pharmaceutical Journal*, July 29, 1899.

dation of the base by chromic acid and the appearance of the green colour of chrome alum. The only other proof of identity required is furnished by a physiological test which could hardly be carried out by the analytical chemist or pharmacist.

The purity is determined by the absence of a residue after ignition. Whilst this test would preclude any inorganic impurity, it would afford no discrimination between pilocarpine and a mixture of the other alkaloids of jaborandi, and indeed the alkaloid might be accidentally or intentionally mixed with an organic impurity and still meet the Pharmacopœia requirements.

The characters and tests for the hydrochloride, which is official in the U.S.P. and German Pharmacopœia, are better than those given for the nitrate in the B.P., but still leave room for improvement. The hydrochloride is described as consisting of "white deliquescent crystals, easily soluble in water and alcohol, sparingly soluble in ether or chloroform." As this salt is exceedingly soluble in the two former solvents, the general statement is sufficient.

The melting point is given as 197° in the U.S.P., and the usual reactions for alkaloid and the inorganic acidulous radical are required as proof of identity. The freedom from inorganic impurity is ensured by the ignition test.

The chromic acid colour reaction is given in the U.S.P., but not in the German Pharmacopœia, but both give a test which distinguishes this from most other alkaloids, including most of the associated alkaloids of jaborandi.

This test is the non-formation of a precipitate on the addition of ammonia to an aqueous solution of the salt. A solution of sodium hydrate gives a precipitate only with a concentrated solution of the alkaloidal salt.

Allen ('Organic Analysis,' **3**, pt. iii., p. 37) states that the alkaloid gives no reaction with picric acid, but I have found that a yellow precipitate of the picrate is thrown down, which dissolves on warming, then separates out in needles on cooling.

Paul and Cownley (*Ph. J.*, **57**, pp. 1, 437) have made some important observations with regard to the pilocarpine nitrate and hydrochloride of commerce. They found that commercial specimens of pilocarpine nitrate were far from pure, three samples examined melting at 141.7° , 150.5° , and 167.2° respectively; further, the crystallised nitrate obtained by them from different kinds of jaborandi leaves melted at different temperatures, viz., from 151.5° – 162.7° , but no proof was adduced that these were the melting points of pure chemical substances. According to these chemists,

a salt described as "pure pilocarpine nitrate" melted at 141.7° , and when recrystallised from alcohol in different fractions gave no considerable alteration in the melting point. They have also examined samples of pilocarpine hydrochloride on the market and found indications of the presence of more than one alkaloid. They remark that a possible explanation given, viz., that the impurity present was jaborine, requires more definite proof.

Petit and Polonowsky* have examined the salts of pilocarpine and give the following constants:—

Pilocarpine nitrate	{	Prisms soluble in 7 parts of water at 18° , in 146 parts alcohol (95 p.c) at 18° . Melting point 177° - 178° $[\alpha]_D = + 82.2^{\circ}$.
Pilocarpine hydrochloride	{	Anhydrous prisms, soluble in 0.4 parts of water, in 10 parts alcohol. Melting point 200° . $[\alpha]_D = + 91^{\circ}$.

They also state that commercial specimens examined contained an impurity, stated to be pilocarpidine, to as large an extent as 50 per cent.

These results, however, relate to chemically pure products, and it is not always advisable to insist on this degree of purity for chemicals required for medicinal use, owing to the extra expense incurred not being commensurate with the corresponding therapeutic advantage.

These results, therefore, required confirmation and also investigation as to the ease with which such impurities are removed, and the effect of small amounts of such impurity on the physical constants of the pure salt. The question has also been raised as to the identity of the alkaloid pilocarpine, when obtained from different species of jaborandi leaves, the results of Paul and Cownley being insufficient to answer this question.

In the present communication I give a method for determining the amount of pilocarpine in the total alkaloid, then proof of the identity of pilocarpine from different sources, and finally the characters and tests for pilocarpine nitrate and hydrochloride.

ASSAY OF PREPARATIONS CONTAINING PILOCARPINE.

Several methods are available for extracting the total alkaloid from jaborandi or its preparations, and any of these may be used to obtain the mixture of amorphous bases.

The varnish obtained is dissolved in a small quantity of a saturated alcoholic solution of pilocarpine nitrate, and to this solution is

* *Journ. de Pharmacie* [6], 5, 370, 430, 475, and [6], 6, 8.

added a strong alcoholic solution of nitric acid (freshly prepared) until the solution is faintly acid, and it is then set aside to crystallise, after the addition of a small crystal of pilocarpine nitrate. It is then allowed to stand for two hours without concentration, stirred vigorously, and any crystals which have separated are filtered off, drained by the filter pump, washed with the saturated alcoholic solution of pilocarpine nitrate, dried and weighed. If no crystals separate the total alkaloid contains not more than traces of pilocarpine.

From the weight of crystalline nitrate thus obtained, the percentage of bases in the total alkaloid yielding crystalline nitrate can be calculated.

It is sufficient in most cases to assume this to be pilocarpine but if a very accurate determination be required the melting point and specific rotation of the nitrates should be determined, and from these data can be calculated the amount of pilocarpine present. My experience, however, is that it is quite sufficient to take the melting point, and as this is generally above 170° , the calculation can be made on the assumption that the crystalline nitrates consist entirely of pilocarpine. Assuming the other impurity to be pilocarpidine, and the constants given for that salt by Petit and Polonowsky to be correct, the percentage of pilocarpine present could be determined from the specific rotation of the mixed nitrates by the following formula:—

$$p = \frac{100}{43.7} (x - 38.5)$$

When p = percentage of pilocarpine present in mixture, x = specific rotatory power of salt examined.

Good results will be obtained by this method of assay if as much as 0.5 Gm. of total alkaloid be taken.

The melting point will also serve as an indication of the proportion of pilocarpine present, if above 174° it may be calculated as pure pilocarpine, if from $167^{\circ} - 174^{\circ}$ from 80 – 90 p.c. pilocarpine.

If the product melts below 167° it should be recrystallised from a small quantity of hot absolute alcohol and the weight taken of the crystalline nitrate thus obtained, and proceeded with as above. Whilst not claiming that this method gives results comparable in accuracy either with the methods for inorganic or organic analysis, or even those for determining the amount of total alkaloid, yet I do claim that it is more important to know, within limits of even 5 per cent., the amount of pilocarpine in the total alkaloid than to

be able to determine the latter factor with greater accuracy, since this figure gives us absolutely no information as to the amount of pilocarpine present, whilst the method described does so within the limits of experimental error above indicated

CHARACTERS OF PILOCARPINE NITRATE AND HYDROCHLORIDE.

In order to be certain of the identity of pilocarpine nitrate from various sources, I prepared the salt from two varieties of *aborandi* leaves, viz., the true *jaborandi* and the small leaved variety, *Maranham jaborandi*, and I also purified some pilocarpine nitrate purchased from two manufacturers. I found that, contrary to the statements of Paul and Cownley, and Petit and Polonowsky, the nitrate is easily purified by repeated recrystallisation from strong alcohol, and this method was used to purify the salts.

The proof of the identity of the pilocarpine nitrate prepared from these different sources and of its chemical purity was furnished by the fact that the salt, after several recrystallisations from different solvents and when obtained in different fractions, underwent no change in the melting point or specific rotatory power, and that the physical constants of the purified salt from every source were identical. The physical constants of the pure salt were :—

	Jowett.	Petit and Polonowsky.
Melting Point	178°	177 - 178°
[α] _D +	82.9°	+ 82.2°
Solubility in water.	1 in 6.4 (at 20°)	1 in 7 (at 18°).

A further proof of the identity of pilocarpine nitrate as obtained from different sources is furnished by the agreement of the factors obtained by me and those given by Petit and Polonowsky.

I am unable to understand why a sample of pilocarpine nitrate, melting point 141.7°, when recrystallised from alcohol in different fractions should give no alteration in the melting point, as I obtained the following results with a commercial specimen melting at 168°, and I have never met with a preparation with a lower melting point than 167°.

Melting points of pilocarpine nitrate after recrystallisation from alcohol :—

Melting point of original salt	=	168°
After first recrystallisation	=	175°
„ second „	=	176°
„ third „	=	176°
„ fourth „	=	178° and [α] _D = + 82.94°

The specimen referred to by Paul and Cownley must have been very impure

I am able to confirm the observations of other chemists that the pilocarpine nitrate of commerce is impure. Two specimens were examined by me from different manufacturers, and both yielded by recrystallisation about 85 p.c. of pure pilocarpine nitrate.

The examination of these specimens gives the following results:—

A. Melting point	167°	.	[α] _D	=	+	77·88°
B. Melting point	168°	.	[α] _D	=	+	79·08°

The impurity consisted of a crystalline nitrate of much lower melting point and specific rotatory power. This would appear to be possibly pilocarpidine nitrate, but I am not in a position at present to state whether this is the case.

Pilocarpine hydrochloride was prepared in the usual way through the base from pure pilocarpine nitrate, and then purified by repeated recrystallisation till the melting point and specific rotatory power were unchanged by further treatment.

The pure salt had the following physical constants:—

	Jowett.	Petit and Polonowsky.
Melting point =	204 — 205	200°
[α] _D	+ 91·74°	+ 91°

I attribute the higher figures obtained by me to the greater purity of the salt examined, as, though made from pure pilocarpine nitrate, it melted at 202°, but after recrystallisation at 204-205°.

The hydrochloride described by Paul and Cownley as melting at 192°-196° must have been impure, but there is no reason to suppose that this impurity was different from that found in the nitrate, and stated to be pilocarpidine, as I have found that the nitrate of low melting point obtained from commercial pilocarpine nitrate yields a hydrochloride melting below 200°; this would be a likely impurity. Having thus determined the physical constants of the pure substances I am able to suggest characters and tests for these salts. With regard to their purity I should not recommend that absolute purity be required, as the removal of the last traces of the other alkaloid requires an amount of recrystallisation out of proportion to the amount of impurity originally present. A nitrate melting at 175°-176° would not contain more than 1 per cent. of impurity, but would require three or more recrystallisations to be completely purified.

I would therefore suggest the following characters and tests:—

Pilocarpine Nitrate.—White distinct crystals, permanent in the

air. Soluble in 6 to 7 parts of water at ordinary temperatures, and in 146 parts of cold alcohol (95 per cent.), and fairly soluble in boiling alcohol; almost insoluble in ether or chloroform.

When heated in a capillary tube the salt melts at 176° to 178° . The specific rotatory power in aqueous solution should be $+ 81^{\circ}$ to $+ 83^{\circ}$. On ignition the salt yields no residue (absence of inorganic impurity). A concentrated aqueous solution gives no precipitate on the addition of ammonia water or aqueous solutions of sodium or potassium hydrate (distinction from most other alkaloids). Affords the characteristic tests for nitrate.

Pilocarpine Hydrochloride.—White crystals, deliquescent in damp air. Soluble in less than its own weight of water, and in 10 parts of absolute alcohol; almost insoluble in ether or chloroform.

When the salt, dried at 100° , is heated in a capillary tube, it melts at 200° to 204° .

The specific rotatory power in aqueous solution should be $+ 90^{\circ}$ to $+ 92^{\circ}$. On ignition the salt yields no residue (absence of inorganic impurity). A concentrated aqueous solution gives no precipitate on the addition of ammonia water, and only a few oily drops, on the addition of aqueous solution of sodium or potassium hydrate, which quickly redissolve (distinction from most other alkaloids). Affords the characteristic tests for chlorides.

These characters and tests would ensure such a product as would seem suitable for medicinal use; but if it be thought desirable that the chemically pure salts should be used, then the constants given for these salts must be used.



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