# PSEUDOEPHEDRINE FROM CHINESE EPHEDRA

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In preparing pure Ephedrine hydrochloride from Chinese Ephedra it was found that instead of using Chou's oxalate method (3), a pure product could be obtained by simply washing the crude salts with chloroform and recrystallizing the residues. When this method was published (7) it was known that the chloroform removes almost completely the colored impurities, and recrystallization gives the pure ephedrine hydrochloride salt. No attempt was then made to isolate the pseudoephedrine from the mother liquids. However Chou from the alcoholic mother liquors from the preparation of ephedrine hydrochloride obtained pseudoephedrine which represented 20 per cent of the total yield of alkaloid.

Chen and Kao (2) have now stated that, "It appears, therefore, probable that the plant *Ephedra vulgaris* var. *helvetica* yields ephedrine when grown in China but pseudoephedrine when grown in Europe. Such analogy can be found in oil of turpentine.....Chen extracted the base after making the solution alkaline with ammonium hydrate." This is certainly not the case as is readily understood if one considers Chou's (3) results which show a content of 20 per cent of the total alkaloid of pseudoephedrine in Chinese Ephedra, and the obvious fact of the decades old European manufacture of ephedrine from the Swiss plant. This has been recently confirmed in a private communication from E. Merck in which is stated, "I ought to add here that as regards obtaining supplies of raw material I was restricted to Southern Europe.....I am being supplied with a drug which, contrary to opinions expressed elsewhere, yields chiefly ephedrine and but little pseudoephedrine."

Furthermore it should be noted that it is now well established that the Chinese ephedra is not *Ephedra vulgaris* var. *helvetica*, instead of which we have the original botanical identification by Cowdry (5) of the Peitaiho plant as being *E. equisetana* Bunge, and Liu's (10) description of the Mongolian plant for which Stapf has suggested the name *E. sinensis* (6). Fuller botanical reports are expected this autumn which will more clearly show the pronounced botanical differences between the Swiss and Chinese ephedras.

Whilst it is true that Miller (11) was only able to isolate pseudoepedrine from Swiss ephedra, which we can readily explain in the following experiments, E. Schmidt (12) who subsequently worked so much upon these alkaloids summarizes the whole by stating that ephedrine is the alkaloid obtained from *Ephedra vulgaris* var. *helvetica*.

The Laboratory of the American Medical Association (4) noted, when testing for the melting point of ephedrine base shaken out by the usual method for removing alkaloids, that there is a reaction with the chloroform so that the hydrochloride is obtained instead of the free alkaloid, and the melting point of 39°C is then erroneously reported as 210°C. We have made a particular study of the solubility of ephedrine hydrochloride in chloroform, and of various assay methods, and find that in the total alkaloidal assay the ammoniacal chloroformic extract is chiefly pseudo ephedrine hydrochloride, and that when pure ephedrine salts are used the chloroform can extract very little unless as proposed by Chou *ammonia be replaced by potassium carbonate, or as we have found the ammonia must be in very great excess, far more than "alkaline to litmus."*

In the first trial experiment to prepare pseudoephedrine from Peking ephedra, an attempt was made to free the crude alkaloid from colored impurities by washing with chloroform, with the surprising result that the residue free from colored impurities was practically pure ephedrine hydrochloride, and the washings contained the dextro-rotatory fraction of pseudoephedrine hydrochloride.

The occurrence of ephedrine and pseudoephedrine in the crude drug and the *clear cut separation of their hydrochlorides by chloroform* provides an easy method of preparation and explains some of the ambiguities surrounding their alleged melting points and the failures to obtain satisfactory assay of the crude drug (13).

## EXPERIMENTAL

*Manufacture from crude ephedrine.*

As already stated it is possible to separate the pseudoephedrine in Chinese ephedra by making the usual acid extraction of the crude drug, shaking out the alkaloids with potassium carbonate and chloroform, and subsequently when the crude hydrochlorides are obtained to make a clear cut division by washing with chloroform. When the sole object is to prepare pseudoephedrine the following procedure will give a good yield.

The mother liquors and washings from the preparation of ephedrine hydrochloride are evaporated to dryness, washed with ether to remove colored impurities, and air dried. One hundred grams of the dry residue are gently refluxed on an oil bath at 110-130°C for twelve hours with 1 litre of N hydrochloric acid. The solution with the aid of suction is then evaporated to dryness over a water bath, and the residue washed with ether containing ten per cent of alcohol. The dry crude residue is then treated with four litres of chloroform which entirely removes the pseudoephedrine salt and the colored impurities leaving behind unchanged ephedrine hydrochloride.

The chloroformic solution is evaporated to dryness. The dry residue is taken up in two parts of water, there is added four parts of saturated potassium carbonate solution and it is again shaken out with chloroform. The chloroform is evaporated and out of the concentrated solution there crystallizes pseudoephedrine alkaloid.

The pure alkaloid is dissolved in alcohol and neutralized, or made very faintly acid, with hydrochloric acid. By concentration and recrystallization from alcohol pure pseudoephedrine hydrochloride crystallizes out in beautiful needles, which are washed with ether and air dried.

Various trials were made to test out the volume of chloroform required, the advantage or otherwise of making fractional extraction, and methods of purifying the pseudoephedrine base before proceeding to make the salt.

The solubilities of ephedrine hydrochloride and pseudoephedrine hydrochloride were tested and the results amply prove the method and explain other results obtained with mixtures of the salts.

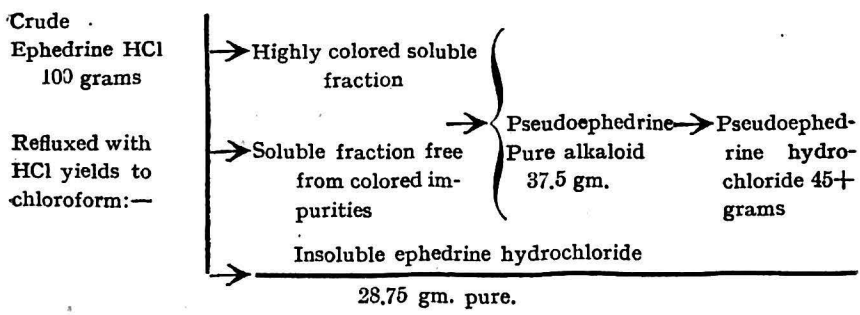
## RESULTS

*Yield of pseudoephedrine and the hydrochloride.*

Starting with 100 grams of the crude ephedrine residues there were obtained 69 grams of the chloroform soluble fraction chiefly pseudoephedrine hydrochloride. Undissolved ephedrine hydrochloride weighed 18.75 grams; this was practically pure giving a melting point 214-215°C and a rotation of -31.25° (theoretical=215-216°C, $\alpha \frac{25}{D} - 32.5°$)

When the orignal washing with chloroform was done fractionally it was possible to divide a preliminary highly colored fraction from a later colorless fraction of 48 grams of nearly pure pseudoephedrine hydrochloride. This salt when treated yielded absolutely pure pseudoephedrine, m.p. 118°C, $\alpha \frac{25}{D} + 50°$ (in absolute alcohol). The highly colored fractions also yielded more of the alkaloid by recrystallizing the crude base either from two volumes of chloroform or from alcohol, and thorough washing with ether.

The purified alkaloid was also used to prepare the pure salt by dissolving in three parts of 95 per cent. alcohol and neutralizing with about one part of 7-N hydrochloric acid, (1 gram of alkaloid requires 6.6 cc 1-N HCl). The solution was evaporated to dryness, the residue redissolved in hot alcohol, filtered, allowed to cool and spontaneously evaporated. Pure pseudoephedrine hydrochloride crystallized out in beautiful needles, which when filtered and washed with ether gave a melting point of 179 to 180°C, and a rotation of +58.75°.




*Solubility in chloroform.*

In order to test fully this method, a careful estimation was made of the solubility in chloroform of pure ephedrine hydrochloride and pure pseudoephedrine hydrochloride.

| | Solubility in chloroform at 25°C | Rotation of solution in chloroform |
|---|---|---|
| Ephedrine hydrochloride | 0.0253 per cent | Not appreciable |
| Pseudoephedrine hydrochloride | 1.3300 „ | +52.0° |

Pseudoephedrine hydrochloride is about 53 times more soluble in chloroform than ephedrine hydrochloride.

In making the original chloroformic washing of the crude ephedrine residues after using the theoretical amount of chloroform which could dissolve the theoretical yield of pseudoephedrine hydrochloride, we washed the insoluble residue further with more than three hundred grams of chloroform and less than half a gram of material went into solution, showing clearly that the pseudoephedrine salt was removed. The following shows how fractional washing with chloroform took up the material:—

| Washing No. | Volume of Chloroform | Weight of material dissolved | M. P. |
|---|---|---|---|
| I | 1200 cc | 20 gm colored | not sharp |
| II | 400 cc | 7 gm sl. color | 156°–158°C |
| III | 800 cc | 18 gm no color | 158°–160°C |
| IV | 1200 cc | 30 gm „ | 160°–162°C |
| V | 400 cc | 0.8 gm „ | not sharp |
| VI | Residue undissolved | 28.75 gm no color | 215–216°C |

## DISCUSSION

The above results show quite clearly how various workers (1,11), in attempting to extract the alkaloids, and to check the melting points of the bases and their hydrochlorides, were liable to go wrong. Firstly as shown by Chou (3) it is essential to use potassium carbonate to liberate the base, and herein is shown how if the mixed hydrochlorides be treated with chloroform the substance obtained is an impure pseudoephedrine salt.

The fact that ephedra contains two alkaloids which in some respects have opposite effects (8), makes it of peculiar interest that old Chinese medical writers should have been so particular about using the stems of the plant freed from the nodes and roots. The Pen T'sao (14) states that, "The root, together with the joints, is considered to have an action directly opposed to that the stem, and is therefore prescribed in profuse sweating." The Kuang Ch'un Fang P'u (9) in describing the method of the drug directs that the drug be collected after the beginning of autumn. The nodes and roots should be discarded, because the nodes are antidiaphoretic. "Make a decoction and raise to the boil ten times, each time removing the surface scum with a bamboo stick, for the scum is depressant in its action". These statements suggest that in the plant there is an uneven distribution of active principles. It will be of great interest to analyse the joints apart from the stems to ascertain the nature of their alkaloidal content.

## SUMMARY

1. The facts are set forth showing that both Chinese and Swiss Ephedras contain both pseudoephedrine and ephedrine, and the method of manufacture of these alkaloids is further elaborated to produce a large yield of pseudoephedrine.

2. The solubility of pseudoephedrine hydrochloride in chloroform is found to be about fifty three times as great as ephedrine hydrochloride.

3. The difference in solubilities in chloroform of the hydrochloride salts of ephedrine and pseudoephedrine provides a clear cut method of separation for the preparation of these two alkaloids.

4. The difference in solubilities in chloroform of the hydrochloride salts of ephedrine and pseoudoephedrine, and the inability of a small excess of ammonia to liberate the bases from these salts may account for the many erroneous statements concerning the occurrence of these alkaloids in the various Ephedras, also for the low assay results reported.

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# 國產麻黃中之麻黃副素


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中國麻黃與瑞士麻黃均含麻黃素與麻黃副素。提製之法亦經改良，故麻黃副素之製出量可以加多。

鹽酸麻黃副素能溶於哥羅芳之量，約五十三倍於鹽酸麻黃素。提製之時，可利用此法，使麻黃副素與麻黃素分離。

前此各種報告，對於麻黃所含此類鹼質及成分均甚低。蓋因鹽酸麻黃素與鹽酸麻黃副素在哥羅芳內溶化率之不同，及鹼之不能由此二素之鹽酸合質而分出其基質故也。