ABSTRACT OF DISCUSSION.

H. Engelhardt stated that one of the reasons for presenting this paper was to induce further research; it may be possible that the estimation is based on wrong fundamental principles.

Wilbur L. Scoville said he had tried the method of the paper, and that the reaction is faulty; in one trial with it on the same lot of tablets he obtained results corresponding to 100 percent, while another test only showed 60 percent; the reaction is not constant. He was asked by Mr. Engelhardt whether he had made use of hydrogen peroxide; in reply, he insisted that the reaction was fundamentally wrong. Mr. Engelhardt acknowledged this. Continuing, Mr. Scoville stated: that the objection to the colorimetric method is that the results of individuals differ; not as much difference in results of to-day as of a few years ago, because there is a better technique. The knowledge and experience of colorimetric methods, like anything else, must be learned. If better methods can be devised, let us have them.

It was voted that the paper be published.

THE INFLUENCE OF ACID IN THE EXTRACTION OF CINCHONA.*

BY WILBUR L. SCOVILLE.

Experiments on the extraction of cinchona with acidulated menstrua have been continued, the purpose being to secure, if possible, a more reliable menstruum or an improved method.

In the present series cinchona calisaya was used, 250 grammes being employed in each experiment. The usual mode of procedure was to moisten the drug with the menstruum in the standard way, pack in a percolator, flood with the menstruum, then macerate 48 hours. Percolation was then started, the first 200 Cc. reserved, then percolation was continued until 1000 to 1200 Cc. more of percolate had been collected. The first 200 Cc. were assayed, the weaker portion evaporated to a soft extract, this dissolved in the first reserve, and the final volume adjusted to 240 Cc. (190 + 50). The drug used assayed 5.30% of total alkaloids.

Experiment 1. Menstruum, alcohol 200, glycerin 15, hydrochloric acid 10, then alcohol 4, water 1. The first 200 Cc. showed 3.02% of alkaloids, equivalent to 57% of exhaustion. The finished product assayed 4.60% of alkaloids, indicating 86.8% exhaustion.

The residue in the percolator was dried and assayed, being found to contain 0.9% of alkaloids.

Experiment 2. The same menstruum was used, but the percolation was conducted with a hot menstruum. The apparatus used consisted of two copper percolators, the smaller being just large enough to hold the 250 grams of moistened drug and fitting into the larger so as to leave a space of about 10 millimeters between the two. A cover clamped to the top of the outer percolator provided for a reflux condenser, and to the lower end of this percolator was fitted a flask holding 1000 Cc. After macerating the drug for 48 hours in the inner percolator the neutral non-glycerinated menstruum was placed in the lower flask, the condenser attached, and heat applied. The hot vapors of the menstruum passed around the percolator containing the drug thus heating it, were then condensed and passed through the drug, then collected in a separate container by means of a side tubulure at the bottom of the percolator. In this way the heat was maintained during the percolation, independently of the rate of flow. The latter was regulated to correspond with the cold percolation—about 12 drops per minute.

The first 200 Cc. assayed 2.67% of alkaloids showing 50.4% of exhaustion, and the finished product 4.92% of alkaloids, showing 92.4% exhaustion.

This suggests a less rapid rate of exhaustion than the cold process, but more complete exhaustion with the same amount of menstruum. The residue in the percolator assayed 0.45% of alkaloids.

Experiment 3. Menstruum, alcohol 200 Cc., concentrated hydrochloric acid 10 Cc., water 15 Cc., then 76% alcohol.

---

* Read before Scientific Section A. PH. A., New Orleans meeting, 1921.

The first 200 Cc. assayed 2.85% of alkaloids, equal to 54% exhaustion and the finished product assayed 4.70, indicating 88.7% of exhaustion. It may be noted that this corresponds to the first experiment except that no glycerin was used in the menstruum, and the results are about the same as in the first experiment.

Experiment 4. 250 grammes of drug were thoroughly wetted with a mixture of 65.8 Cc. of hydrochloric acid and 187.5 Cc. of water, allowed to stand over night, then the drug was spread out and dried at a low temperature—about 40° C. This dried drug was then treated in the same way as fresh drug, using 76% alcohol as menstruum (alcohol 4, water 1). The first 200 Cc. assayed 1.55% of alkaloids, indicating 30% of exhaustion, and the finished product assayed 4.70%, showing 86.8% of exhaustion.

Experiment 5. This was conducted in the same manner except that the first maceration was made with a mixture of 32.9 Cc. of hydrochloric acid and 217 Cc. of water. The first 200 Cc. assayed 1.38% of alkaloids, indicating 26% of exhaustion and the finished product assayed 4.8% of alkaloids, showing 90% exhaustion.

It will be noted that in these two experiments a large excess of acid was used in the preliminary treatment of the drug, followed by a neutral non-glycerinated menstruum on this treated drug.

Experiment 6. The drug was first macerated and percolated with 250 Cc. of 76% alcohol, then the percolation continued with the same strength of alcohol containing 30 Cc. of hydrochloric acid in each 1000 Cc. of menstruum. Here the acid was used to obtain the weak percolate instead of the strong. The first 200 Cc. assayed 1.75% alkaloids, indicating 33.3% exhaustion, and the finished product assayed 4.7% alkaloids, showing 86.8% exhaustion.

Experiment 7. The drug was exhausted by percolation with sufficient of a mixture of 50 Cc. hydrochloric acid and 950 Cc. of water, the percolate evaporated to a soft extract, then taken up with 78% alcohol. The finished product assayed 3.4% alkaloids, showing 63.6% exhaustion.

Experiment 8. The drug was exhausted by *hot* percolation with a mixture of 15 Cc. hydrochloric acid and 985 Cc. of water, the percolate evaporated to a soft extract and taken up with 76% alcohol.

A progressive tendency of the drug to clog was noted in this process, as also in the hot percolation with alcoholic menstruum. The heat appears to harden the drug, and the last portions of percolate came through very slowly, requiring a removal of the mass from the percolator and repacking to secure a reasonable rate of flow.

The finished product assayed 3.2% alkaloids, showing 61% of exhaustion.

Experiment 9. The drug (250 Gm.) was first macerated in a mixture of 5 Cc. lactic acid in 200 Cc. of 76% alcohol, then percolated with 76% alcohol. The first 200 Cc. assayed 1.6% alkaloids, equivalent to 30% exhaustion. The finished product assayed 2.9% alkaloids, showing 54% exhaustion.

Experiment 10. The drug was first macerated in a mixture of 5 Cc. lactic acid in 200 Cc. of 76% alcohol, then percolated with a mixture of 20 Cc. hydrochloric acid in 980 Cc. of 76% alcohol.

The first 200 Cc. assayed 1.8% alkaloids, indicating 34% exhaustion. The finished product assayed 4.5% alkaloids showing 83% exhaustion. Evidently lactic acid is not as efficient as hydrochloric in exhausting cinchona, although the lactates are the most soluble of these alkaloidal salts.

Experiment 11. The drug was macerated and percolated with 1500 Cc. of menstruum consisting of 76% alcohol containing 15 Cc. of hydrochloric acid. The first 200 Cc. assayed 1.97% alkaloids, indicating 35% exhaustion. The finished product assayed 3.6% alkaloids, showing 66% exhaustion.

Experiment 12. Alcohol of 94% strength was used as menstruum, to the first 250 of which were added 10 Cc. of hydrochloric acid. The first 200 Cc. assayed 2.00% alkaloids, indicating 37% exhaustion. The finished product assayed 3.8% alkaloids, showing 72% exhaustion.

Experiment 13. Diluted alcohol was used as a menstruum, the first 250 Cc. containing 10 Cc. of hydrochloric acid. The first 200 Cc. assayed 2.48% alkaloids, indicating 46% exhaustion. The finished product assayed 5.00% alkaloids, showing 92% exhaustion.

In all these experiments it will be noted that hydrochloric acid aids extraction and that it is most effective when used in definite proportion.

Thus in the first three experiments the drug was first macerated in a 76% alcoholic menstruum containing 1.6% of absolute hydrochloric acid, then followed by a neutral alcoholic menstruum. These all show more than half the total amount of alkaloids in the first 200 Cc. of percolate, and a final exhaustion of 86 to 92%.

In the next series the drug was first macerated in 10% and 5% aqueous hydrochloric acid, then dried, and the dried drug, now freed from the excess of acid, percolated with a neutral alcoholic menstruum. But this treatment does not appear to favor exhaustion, for the first 200 Cc. of percolate shows only 30% and 26% of exhaustion and the final product 86.8% and 90% exhaustion.

It is noticeable here that the very large excess of acid shows a retarding action on extraction. This indicates that there is an optimum concentration of acid which produces the best results, and that concentrations above or below this are less efficient.

This fact was further shown in another way. In the assays of the drug marcs remaining after Experiments 1 and 2 the marcs were treated with 30 Cc. of 10% HCl and 30 Cc. of 5% HCl for 15 Gm. of the drug. The first showed 0.4% of alkaloids and the second 0.52%. In the second case a result of 0.68% and 0.9% was obtained. In other words the 10% acid actually prevented a full extraction of the alkaloids.

The third series made the initial extraction with a neutral menstruum, then followed with 1.25% acid-alcoholic menstruum. Here the first percolate shows only 33% of exhaustion, but the final product shows 86.8%.

The next series used acid-water only as the menstruum, one extracting with cold 2% hydrochloric acid, the other with hot 0.6% acid. In these cases much larger quantities of percolate were collected, percolation being continued until the liquid came through but slightly bitter. It is noticeable that the drug exhausts slowly with an aqueous menstruum—and in the hot process the action of hot hydrochloric acid on tannins, forming phlobaphene, is undoubtedly a factor. The residue obtained after evaporation of the acid-aqueous extract is tough and insoluble in water. The extraction of this by the alcoholic menstruum is difficult and undoubtedly accounts in part for the low results. In Experiment 8 this residue was finally dried thoroughly and powdered, then macerated in the menstruum for 24 hours before filtering.

In the next series lactic acid was tried, on the theory that this acid would have less action on the tannins and might be a better solvent for the alkaloids. But the result shows no aid whatever from the lactic acid but again an advantage from the hydrochloric.

A weak—0.4% acid—alcoholic menstruum was then tried throughout the extraction. This resulted in only one-third exhaustion in the first percolate and only two-thirds in the final product. Here again is shown that it is not the total *quantity* of acid which is used but its concentration which counts in extraction.

The last experiments were intended to find more about the influence of the alcoholic strength of the menstruum. One menstruum consisted of 95% alcohol containing 1.6% of hydrochloric acid in the first maceration, and the other of diluted alcohol (49%) used in the same way. The strong alcohol shows 37% and

72% of exhaustion and the diluted alcohol 46 and 92%. This indicates that alcohol is less of a factor in extracting the alkaloids of cinchona than acid, though it may be more of a factor in maintaining a clear solution. The experiments reported a year ago show plainly that in alcoholic menstruum acid is an important factor in maintaining a clear solution.

Regarding the stability of the present series the first two experiments in which a 1.6% hydrochloric acid in 76% alcohol formed the first menstruum, there is but little sediment in the bottles after 5 months' standing, and the glycerin does not appear to have a material influence. With the same menstruum used hot, about three-quarters of an inch of sediment shows in an 8-ounce bottle.

The next two, wherein the drug was first treated with 5 and 10% aqueous acid and then dried, about a third of an inch of dense sediment appears after 4 months' standing.

The next series—extraction with aqueous acid and a subsequent extraction of this evaporated extract with 76% alcohol—shows only a slight precipitation after 4 months in the cold process. The hot method has not yet stood long enough to judge of its stability.

The lactic acid extractions show about one-quarter inch of precipitate in the first and half as much in the second—the latter containing hydrochloric as well as lactic acid.

The next sample—extraction having been made with very weak hydrochloric acid—shows half an inch of dense precipitate. And when 94% alcohol was compared with 49% as a menstruum, we find abundant precipitates adhering to the sides of the bottles, but much larger in the weaker alcohol than in the stronger.

Apparently, the 76% alcohol which has been adopted as the menstruum is the best strength both for extraction and for stability. And the addition of hydrochloric acid to this undoubtedly helps both factors.

SUMMARY.

The present status of the investigation may be summarized as follows:

1. Hydrochloric acid, used in proper proportion with 78% alcohol materially aids extraction of the alkaloids.

2. The best results have been obtained when the first portion of the menstruum contained about 1.6% of hydrochloric acid. Much stronger or weaker acid than this gave lower results.

3. The acid-containing extract should not be heated because this changes tannin to insoluble phlobaphene, which precipitates and appears to entangle the alkaloids. Hence the acid should be used in the initial maceration, or to obtain the stronger reserve extract only.

4. Lactic acid is not as efficient as hydrochloric; in fact, shows no advantage in extraction.

5. Hydrochloric acid stabilizes the fluidextract by reducing precipitation very markedly.

6. The complete extraction of cinchona is slow and tedious. The last 10 to 15 percent of alkaloids comes out reluctantly, necessitating the use of a large quantity of menstruum to extract it.

LABORATORY OF PARKE, DAVIS & COMPANY,
DETROIT, MICHIGAN.

ABSTRACT OF DISCUSSION.

The author stated, in reply to a question, that powders of same degree of fineness had been used in the extractions, also the same drug and approximately the same amount of menstruum.

The discussion on the paper was somewhat concerned with the therapeutic value of the alkaloids that remained in the marc; J. P. Snyder suggested that these may be amorphous and have no therapeutic value. The assay of the U. S. P. might be misleading to that extent.

Hugo H. Schaefer stated that the final extractions of cinchona give a larger yield of chinoidin than the first, but the last extractions contain crystalline alkaloids; if they did not, these extractions would not be made. The determination of total alkaloids depends largely on the assay process employed; there may be a question as to whether the assay or the extraction process is faulty; nux vomica can be completely extracted of its alkaloids, to the extent of a marc without bitter taste.

Arno Viehoever stated that there was a portion of a cinchona alkaloid so absorbed in the plant cells that it cannot be extracted.

Lyman F. Kebler said that he had never been able to obtain 100% assay results with cinchona, but he had with ipecac.

THE ALKALOIDAL STANDARD OF FLUIDEXTRACT OF IPECAC, U. S. P.*

BY FRANTZ F. BERG.

The U. S. P. VIII standard for alkaloidal content of Ipecac was 1.75% total ether-soluble alkaloids for Rio Ipecac, and the standard alkaloidal content for Fluid Extract Ipecac U. S. P. VIII was 1.5 Gm. for each 100 Cc. thereof.

In the U. S. P. IX Cartagena ipecac has been included with the Rio variety. The Cartagena variety has been shown to assay higher in alkaloids than the Rio variety. Thus with both varieties official, it was decided not to change the standard of alkaloid content, permitting the use of either.

For some reason, unknown to the writer, the standard of fluidextract of Ipecac was changed from U. S. P. VIII requirement of 1.5 Gm. to 100 Cc. of product to requirement of 1.8 Gm. to 2.2 Gm. for each 100 Cc.

Possibly it was believed that through the admission of the Cartagena Ipecac this standard could be obtained.

It is also worthy of note that the menstruum for fluidextract of Ipecac was changed in the U. S. P. IX; whereas the former edition specified a menstruum of approximately 71% alcohol, the U. S. P. IX specifies a menstruum of about 37% alcohol, this change having been instituted in an attempt to render the fluidextract miscible with syrup in the preparation of syrup of Ipecac.

Numerous attempts have been made, using varying proportions of alcohol in the menstrua, for exhausting the drug, and while the product of a 37% alcohol permits of miscibility with syrup, it has been shown[1] that it is extremely difficult to effect exhaustion with alcohol of that strength. Ipecac appears to resist all efforts to obtain complete exhaustion by the use of any alcoholic menstruum. This problem of Ipecac extraction is one which confronts every maker of fluidextracts, and, in an attempt to determine if the yield of fluidextract might be increased, some coöperative work[2] has been done—the result being a yield of 83% of fluidextract from the drug.

---

* Read before Scientific Section A. Ph. A., New Orleans meeting, 1921.

[1] JOURNAL OF AMERICAN PHARMACEUTICAL ASSOCIATION.

[2] Proceedings American Drug Manufacturers' Association, 1921.