Construction of Physical Instruments," Geneva, Switzerland. The radius of the tube was found to be 0.0360 cm. This value represents the average result of five independent observers. The average of the elevations was found to be:

$$h_{20^\circ} = 1.6425 \text{ cm.}$$
$$h_{40^\circ} = 1.5569 \text{ cm.}$$

The computation gave the following values:

$$\gamma_{20^\circ} = 19.80 \text{ ergs.}$$
$$\gamma_{40^\circ} = 18.316 \text{ ergs.}$$

Index of Refraction.—By Abbe refractometer:

$$n_{20^\circ} = 1.3895.$$

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1. Oleoresin of Some Western Pines, A. W. Schorger. *Bull.* 119, Forest Service.
2. See letter of C. Stowell Smith to E. Kremers, also laboratory notes of R. J. Harnon.
3. Personal Communication.
4. See letter from C. Stowell Smith to E. Kremers, Dec. 2, 1912.
5. Schorger, *Bull.* 119, Forest Service.
6. *Pharm. Rev.*, vol. 25.
7. *Bulletin* 119, Forest Service.
8. Inasmuch as some of the cans were not very carefully sealed, the average yield may have been lowered somewhat by evaporation.

THE INFLUENCE OF HYDROCHLORIC ACID ON CINCHONA PREPARATIONS.*

BY WILBUR L. SCOVILLE.

It has been observed that in the extraction of cinchona with acidulated menstrua, erratic results are sometimes obtained. In some instances the alkaloids are extracted rapidly and in others very slowly, and that under seemingly parallel circumstances. While the very slow extractions are comparatively rare, they are frequent enough to warrant an investigation. The following experiments were therefore undertaken.

Five hundred grammes of cinchona calisaya assaying 7.1 percent of alkaloids by the U. S. P. process, was percolated with a neutral menstruum consisting of 4 volumes of alcohol with 1 volume of water, and another portion of 500 grammes was percolated at the same time with an acidulated menstruum of the same alcoholic strength but containing 50 mils of diluted hydrochloric acid in the first 500 mils of menstruum. Percolation was conducted as evenly as possible and the percolates received in 400 mil, then 500, 500, 500 and 500-mil portions. Each fraction was then assayed for alkaloidal strength, and the results are as follows:

	Neutral menstruum.		Acid menstruum.	
	Gm. per 100.	% of exhaustion.	Gm. per 100.	% of exhaustion.
First 400 mils	4.2	47.5	5.0	56.5
First 500 mils	1.4	19.77	1.7	24.0
Second 500 mils	0.65	9.25	0.61	8.64
Third 500 mils	0.25	3.53	0.26	3.7
Fourth 500 mils	0.112	1.58	0.110	1.55
Totals		81.63		94.39

*Read before Scientific Section, A. Ph. A., City of Washington meeting, 1920.

Here is shown a distinct advantage in the use of acid, in that the drug was exhausted more rapidly and also more completely. After standing 21 months both fluidextracts have deposited a considerable gummy precipitate which adheres to the bottom and sides of the bottle, the only observable difference being that the acid preparation is slightly smaller in quantity and the more flocculent. It is to be noted that these fluidextracts contain no glycerin.

Three tinctures were also made from 200 Gm. of the drug, percolating to 900 mils. One was a neutral tincture, made by percolating with a mixture of two volumes of alcohol and one of water, the second contained 20 mils of diluted hydrochloric acid in the 150 mils of menstruum in which the drug was macerated, and the third 40 mils of acid, the alcoholic strength being the same in all cases. The drug was moistened with the neutral acid menstruum, allowed to stand 24 hours, then percolated in the usual manner. No glycerin was used in these menstrua.

The 900 mils of neutral tincture assayed 1.1 Gm. of alkaloid per 100, showing an exhaustion of the drug of 70.5%, the 0.2% acid tincture assayed 1.37. Gm. per 100, showing 87% of exhaustion, and the acid (0.4%) tincture assayed 1.45 Gm. per 100, showing 91% exhaustion. Here again the advantage of acid in extraction is shown, and a considerable excess of acid is more efficient than less. After standing 21 months there is a slight precipitate in the neutral tincture, much less in the weaker acid, and none in the stronger acid tincture. In this case the acid shows a marked advantage in stabilizing the tincture as well.

Similar experiments were then carried out on red cinchona, assaying 10.5% of total alkaloids, a neutral and acid fluidextract being prepared, using the same process and menstrua as on cinchona calisaya. Following are the results:

	Neutral menstruum.		Acid menstruum.	
	Gm. alkaloids per 100.	% of exhaustion.	Gm. alkaloids per 100.	% of exhaustion.
First 400 mils	4.85	36.77	5.86	44.5
First 500 mils	2.35	22.37	3.37	31.9
Second 500 mils	0.78	7.40	1.30	12.3
Third 500 mils	0.42	4.03	0.41	3.87
Fourth 500 mils	0.18	1.75	0.16	1.50
Total		72.32		94.07

Here again the advantage of acid is shown. To ascertain whether an increase of acid would be of further advantage, 1000 Gm. of the drug was moistened with a mixture of 600 mils of alcohol, 55 mils of 37% hydrochloric acid and 95 mils of water, then percolated with a menstruum of 4 volumes of alcohol and one volume of water.

This tested as follows:

	Alkaloids per 100	Percent of exhaustion.
First 800 mils	5.25	42.0
First 1000 mils	3.45	34.5
Second 1000 mils	0.93	9.33
Third 1000 mils	0.25	3.15
Total		88.98

Here we find a slower rate of exhaustion than when less acid is used. It is not easy to explain this. The acid evidently is not simply concerned with forming soluble and acid salts with the alkaloids, but has an influence also on other constituents. The alkaloids contained in this lot of cinchona would require approximately 12 Gm. of hydrochloric acid to form hydrochlorides, and 10.5 Gm. per 1000 was used in the first extraction and 24 Gm. in the second. Thus in the second acid extraction enough acid was used to convert all of the alkaloids into the acid hydrochlorides, yet extraction was less rapid or complete when less acid was used than would be required to form the normal chlorides.

A possible explanation, suggested by the differences in precipitation in the neutral and acid preparations, would be that the acid causes the tannoid bodies to become insoluble, or less soluble, and that the alkaloids are partially occluded in this process. But an attempt to throw down the tannoids by adding acid to the neutral solutions resulted negatively, and the question is still open. Like the calisaya fluidextracts the fluidextracts of red cinchona show slightly less precipitation in the acid than in the neutral fluidextracts.

Three tinctures were made, using the mixed drugs for Compound Tincture of Cinchona, but no glycerin in the menstruum. The neutral menstruum consisted of two volumes of alcohol and one of water, and the acid tinctures contained 10 mils and 20 mils, respectively, of 10% hydrochloric acid. The neutral tincture assayed 0.875 Gm. of alkaloids per 100, showing 74.6% exhaustion, the lower-acid tincture assayed 0.935 Gm. per 100, showing 80% exhaustion, the higher acid tincture assayed 1.00 Gm. per 100, showing 85.8% exhaustion. In this case increasing the acid added to the efficacy of the menstruum.

There is also shown a very marked difference in precipitation. The neutral tincture has a considerable adherent precipitate, the lesser acid has a slight precipitate at the bottom, and the more-acid tincture has only a faint precipitate on the sides of the bottle. Here again the acid added to the stability of the preparations as well as aided in extraction.

For reasons of stability alone, the use of acid in the fluidextracts and tinctures of cinchona is, therefore, desirable, in preparations of red cinchona as well as yellow. Sufficient acid to convert the alkaloids into normal hydrochlorides should be used, and this will amount to 100 mils of 10% hydrochloric acid per 1000 Gm. of drug. More acid may accelerate extraction, but the difference is not great. Whether more acid will further add to the stability is yet to be learned. Apparently it will, but the examples here are too few to draw conclusions thereon.

It is plain, however, that the addition of hydrochloric acid to the formulas for tincture of cinchona and compound tincture of cinchona is desirable.

The effect of acid was next tried on the assay of cinchona. Each was again assayed by the U. S. P. process and also by treating 5 Gm. of the ground drug with 5 mils of a mixture of one volume of hydrochloric acid (37%) with two volumes of alcohol. The drug was thoroughly moistened with this mixture, and allowed to dry in the air, then treated as in the U. S. P. process. The following results were obtained:

Cinchona calisaya,	U. S. P. process	7.06 and 7.10%
	acid process	6.60 and 6.62%
Red cinchona	U. S. P. process	10.55 and 10.56%
	acid process	9.80 and 9.97%

In each case the acid process gave lower results than the U. S. P., which was quite unexpected. But there was a noticeable difference in the appearance of the alkaloidal residues; those obtained by the acid method were lighter in color and more clearly soluble. The residues were, therefore, dissolved in an excess of deci-normal hydrochloric acid and titrated with fiftieth-normal alkali, using methyl red as indicator.

The calisaya residues gave a fairly sharp end-point and showed 5.72% and 5.76% of alkaloid by the U. S. P. process and 5.95 and 6.12% by the acid process. The red cinchona gave an uncertain end-point, and the results were 8.80 and 8.97% by the U. S. P. process and 9.62 and 9.70% by the acid process. This shows a reversal of the first figures, the acid method giving higher results by titration and showing that the alkaloid obtained is purer than by the U. S. P. method. This was further proved by second trials of the two methods in which the alkaloids were purified by dissolving in an excess of deci-normal acid, the solution neutralized and allowed to stand 24 hours, then filtered and the alkaloids re-extracted, yielding 8.77 and 9.15% by the U. S. P. process and 9.10 and 9.12% by the acid process for red cinchona and 6.8 and 7.05% by U. S. P. and 6.80 and 6.82% by the acid process on calisaya. This again shows that the U. S. P. assay process yields a very impure alkaloidal residue for weighing.

A modification of Fromme's method (acid) was also tried on both drugs. This consisted in mixing 5 Gm. of the drug with 10 mils of diluted hydrochloric acid and 10 mils of water, digesting on the water bath during one hour, then cooling and shaking with 200 mils of ether-chloroform and an excess of sodium hydroxide, the assay being finished as in the U. S. P. process. Calisaya cinchona gave 6.82 and 6.92% gravimetric and 6.07 and 6.25% volumetric, and red cinchona 9.8 and 9.87% gravimetric by this process.

Several modifications of the acid method were tried, consisting of variations in the amount of acid used and the length of time of digestion. The results were within the normal limits of variation in gravimetric assays. The highest result was obtained when 5 Gm. of drug was heated in a mixture of 5 mils concentrated hydrochloric acid and 15 mils of water for one-half hour, then allowed to macerate over night and shaken in 200 mils of ether-chloroform and 10 mils of concentrated (25%) ammonia water. This gave 9.92 and 10.2% of total alkaloids. Evidently the acid method of assay gives more reliable and accurate results than the U. S. P. method. The alkaloidal residues are purer.

The ether-chloroform mixture directed by the Pharmacopoeia is a mixture of two volumes of ether with one of chloroform. This has a specific gravity at 25° C. of 0.983, which is so close to that of water that the aqueous acid does not separate completely and five to eight shakings are required to extract all the alkaloid. It was found that a mixture of 3 volumes of ether with one of chloroform is quite as efficient as a solvent and requires fewer extractions with acid because the acid separates more quickly and completely. This is a decided advantage.

The following method for the assay of cinchona is recommended: To 5 Gm. of powdered cinchona contained in a 250-mil flask, add 15 mils of water and 5 mils of hydrochloric acid. Mix well and digest two hours on the steam bath (or macerate over night). Cool and add 200 mils of a cooled mixture of 3 volumes of ether and 1 volume of chloroform, then add 10 mils of stronger water of ammonia.

Shake frequently during 12 hours, allow to separate, and decant 160 mils (representing 4 Gm. of cinchona). Extract the alkaloids from this by successive shakings with weak sulphuric acid, mix the acid solutions, add an excess of ammonia and extract with successive portions of chloroform. Evaporate (or distil) off the chloroform, add 5 mils of alcohol to the residue, again evaporate, dry at 100° C. and weigh.

SUMMARY.

Hydrochloric acid not only facilitates the extraction of alkaloids from cinchona red as well as yellow, but it also stabilizes the preparations by reducing precipitation. Acid should be used in at least sufficient amount to convert the alkaloids present into normal hydrochlorides. The use of this acid is, therefore, recommended for tincture of cinchona and compound tincture of cinchona, as well as for all fluidextracts and extracts of cinchona. The influence of acid in promoting stability is shown more clearly in another paper.

In the assay of cinchona a preliminary treatment of the drug with hydrochloric acid results in a purer alkaloidal residue for either weighing or titration, hence is more accurate. The results, while less than by the present official process, are more nearly correct. The process is also improved by changing the proportions of ether-chloroform from 2 to 1 to 3 to 1.

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THE FUNCTION OF GLYCERIN IN TINCTURES AND FLUIDEXTRACTS.*

BY WILBUR L. SCOVILLE.

A considerable number of our fluidextracts and tinctures contain a small proportion of glycerin, usually ten percent by volume, which is employed to prevent or reduce precipitation. That it often is efficacious in this respect is beyond doubt. There is also a marked tendency toward an increased use of glycerin for this purpose, and in nearly all cases the glycerin is employed as a solvent, being a part of the menstruum used in extracting the drug.

It has also been observed that, other things being equal, percolation is not as rapid when glycerin comprises a part of the menstruum as when it is absent, and furthermore it is thought that drugs do not exhaust as rapidly when a glycerinated menstruum is employed as when alcohol-water only is used. This latter impression may come from the slower flow of the glycerinated percolate, or it may be that glycerin is not as good a solvent as has been thought.

The question how glycerin acts in preventing precipitation seems never to have been investigated. Does glycerin act through its solvent power? Or does it prevent precipitation by hindering oxidation or other chemical changes in the drug extracts? Or is the added viscosity an important factor? Is it most effective when used in the menstruum or when added to the (over-strength) percolate? These questions are worth investigating. In this paper the investigation has been confined to preparations official in the U. S. Pharmacopoeia and the National Formulary.

*Read before Scientific Section, A. Ph. A., City of Washington meeting, 1920.