THE INFLUENCE OF HYDROCHLORIC ACID IN CINCHONA PREPARATIONS.

THIRD PAPER.*

BY WILBUR L. SCOVILLE.

This subject was first reported[1] in a paper presented at the Washington meeting in 1920. At that time it was shown that the addition of hydrochloric acid to the menstruum in percolating both yellow and red cinchona results in a more rapid and complete extraction of the alkaloids and also that the acid showed a marked influence in reducing precipitation in the fluidextracts and tinctures. It was further shown that the use of acid in the process of assay of cinchona resulted in a purer alkaloid yield and consequently in more correct results.

In a second paper[2] on the same subject presented last year at New Orleans, the strength of acid was further varied and also its manner of use. Lactic acid was also tried. At this time it was shown that not the amount but the concentration of the acid is the principal factor in facilitating extraction, and that there is an optimum strength of acid which produces the best results. Lactic acid was found to be decidedly less efficient than hydrochloric acid for aiding the extraction.

It was found that a strength of about 1.6% of hydrochloric acid, used without heat and in the first portions of the menstruum, gave the best results with yellow cinchona. Heat did not help the extraction materially, and the strength of alcohol used has more influence in stabilizing the fluidextract or tincture than in the extraction.

Most of the work to this time had been done on yellow cinchona, though a little was reported in the first paper on red cinchona. It remained, however, to verify the most promising method on other samples of yellow cinchona and to ascertain the optimum concentration of acid for red cinchona.

The following experiments, additional to those previously reported, have been tried:

1. A yellow cinchona, assaying 6.4% of total alkaloid, was extracted with hot water containing two drachms of hydrochloric acid per quart, or about 0.3% of acid. About 1500 cc of acidulated water was used on 250 Gm. of the drug. The aqueous extract was evaporated to a soft extract, taken up with 76% alcohol and the volume adjusted to 250 cc. The clear fluidextract assayed 3.9% of total alkaloids showing 61% of exhaustion. Here again it is shown that heat and a weak acid give disappointing results.

2. The same drug was extracted with a cold 0.2 per cent. sulphuric acid. Extraction of the alkaloids was so slow that after 4000 cc of percolate were obtained from 250 Gm. of drug and the drug was still far from being exhausted, this plan was abandoned. A weak aqueous solution does not make an effective solvent for cinchona.

3. The drug (250 Gm.) was exhausted in the usual way with 76% alcohol, using no acid. The first 200 cc of percolate assayed 1.125% of total alkaloids, showing 17.6% of exhaustion. The finished fluidextract assayed 2.35% of total alkaloids, showing 37% of exhaustion. Thus fluidextract yielded 18.64 Gm. of dry extractive per 100 cc.

4. The menstruum used for this experiment consisted of (*a*) 250 cc of 76% alcohol containing 1% of hydrochloric acid (absolute); then (*b*) 76% alcohol. The first 200 cc of percolate assayed 2.00% of total alkaloids, indicating 32% of exhaustion, and the finished fluidextract assayed 5.02% of alkaloids, indicating 78% of exhaustion. This yielded 12.96 Gm. of dry extractive per 100 cc.

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[1] JOUR. A. PH. A., 9, 864, 1920.

[2] *Ibid.*, 10, 844, 1921.

5. This menstruum consisted of (*a*) 250 cc of 76% alcohol containing 2 per cent. of (absolute) hydrochloric acid, and then (*b*) 76% alcohol. The first 200 cc of percolate assayed 2.20% of total alkaloids, indicating 34.3% of exhaustion, and the finished fluidextract assayed 5.76% of alkaloids, indicating 90% of exhaustion. This sample yielded 22.16 Gm. of dry extractive per 100 cc.

6. The menstruum consisted of (*a*) 250 cc of 76% alcohol containing 3% of (absolute) hydrochloric acid, followed by (*b*) 76% alcohol. The first 200 cc of percolate assayed 2.05% of total alkaloids, showing 32% of exhaustion, and the finished fluidextract assayed 4.65% of alkaloids, showing 72.6% of exhaustion. This sample yielded 19.86 Gm. of dry extractive per 100 cc.

A comparison of these last four samples shows that the use of 1% acid in the first menstruum practically doubles the rate of exhaustion over that of the neutral menstruum, but reduces the amount of inert extractive. In this case about two-thirds as much extractive was obtained but more than twice the activity. This suggests why the acid menstrua show less precipitation than the neutral. In the next case, increasing the acid in the first menstruum to 2 per cent. materially increased the rate and amount of extractive, resulting in a final yield that represented 90% of the drug, and gave a total of 22% of extractive. This last is more than that obtained from the neutral menstruum, but is far below it in proportion of extractive to activity. On further increasing the acidity to 3 per cent. the rate and amount of exhaustion were again reduced, and also the amount of extractive. The most efficient amount of acid for yellow cinchona is again shown to be between 1 and 2 per cent. and this also shows a marked reduction in the amount of inert extractive.

This series of experiments was then carried out on a sample of red cinchona, using first the neutral menstruum (76% alcohol), then 1%, 2% and 3% hydrochloric acid, respectively, in the first 250 cc of menstruum followed by 76% neutral alcohol. Following are the results. The drug assayed 8.00% of total alkaloids.

	First 200 cc, per cent.	Rate of exhaustion, per cent.	Finished fldext., per cent.	Amount of exhaustion, per cent.	Extractive, Gm. per 100 cc
Neutral	2.87	36.	5.62	70.3	30.12
1% acid	4.62	57.8	7.22	90.3	33.74
2% acid	4.60	57.5	7.70	96.0	39.36
3% acid	5.50	68.7	7.81	97.5	42.04

Here again is shown the marked advantage of acid in the menstruum, and it is also shown that red cinchona will be helped by a higher percentage of acid than is yellow. The extractive in this case increased regularly with the strength, but the influence of the acid on the alkaloids is clearly shown. And the increase in extractive is far below the proportionate increase in strength over the neutral menstruum.

After standing six months all of the preparations of yellow cinchona show a marked precipitate. This is less in the samples containing 1% and 2% of acid than in the neutral samples, while that containing 3% of acid has about five-eighths of an inch of magma in the bottom of an eight-ounce bottle.

The samples of fluidextract of red cinchona have all remained clear to this time. None of these samples contain glycerin.

It is evident that red cinchona requires a larger proportion of acid for extraction and preservation than does cinchona calisaya. And it is again evident that there is an optimum amount of acid for each variety. To use less than the optimum means less efficient extraction and more subsequent precipitation, and to use more than the optimum means the same. For cinchona calisaya the most efficient proportion of

acid is about 1.5% of hydrochloric acid, based upon the weight of drug used and employed in the first or macerating menstruum. For red cinchona the most efficient proportion is 2.5% to 3%, on the same basis.

As shown in a previous paper[1] while hydrochloric acid when used in the right proportions markedly reduces the precipitation, it is not of itself an efficient preventive. The addition of glycerin, of sugar or of glucose all act as protectives in these preparations. The more than sixty cinchona preparations made in 1918 and 1919 with a view to testing the influence of acid and of glycerin and other protectives have all been kept in the laboratory in a diffused light. These have all been reëxamined, with the following results:

All the neutral preparations—fluidextracts of red and yellow cinchona, tincture of yellow cinchona and compound tincture of cinchona—now contain a heavy precipitate. Those containing glycerin (10% in the fluidextracts and 7.5% in the tinctures) all contain much less but in most cases show at least a small precipitate. Those containing sugar or glucose in the same proportions as of glycerin in corresponding samples, all compare favorably with the glycerinated samples. In other words, glycerin sugar and glucose all act as protectives in cinchona preparations and are almost equally efficient. A slight advantage is seen in glycerin, and glucose is slightly less efficient than sugar but the differences are not very marked.

The acid preparations all show less precipitation than the neutral, and again the addition of glycerin or sugar or glucose is of advantage. Most of the preparations made four to five years ago with acid and preserved by the addition of glycerin or sugar are now clear or very nearly so. Further, these preparations show that the finished preparation should contain its full proportion of glycerin (or sugar) as well as of alcohol. In other words, in diluting a fluidextract or tincture to its standard alkaloidal strength, the diluting liquid should be adjusted so that the finished preparation will contain its full quota of glycerin as well as of alcohol. By so doing precipitation is reduced to a minimum—or entirely prevented.

SUMMARY.

More than 75 experiments have been made on cinchona preparations with a view to learning the best menstruum and process of manufacture for them. As a result of these the following conclusions are drawn:

1. The present official menstrua for the official preparations of cinchona contain the best proportions of alcohol for these. Glycerin is also advisable, but is better added to the percolate or concentrate rather than used in the menstruum.

2. Hydrochloric acid aids very markedly in extracting the alkaloids of cinchona and should be used in the following proportion and manner:

For cinchona calisaya a 1.5% solution of (absolute) hydrochloric acid in the official menstruum (without glycerin), this amount of acid to be based on the quantity of drug used and employed in a corresponding quantity of menstruum used for the initial maceration. Percolation is then continued with a neutral menstruum. Thus for 100 Gm. of drug, the first 100 cc of menstruum used should contain 1.5% of hydrochloric acid, and the drug macerated in this for 24 to 48 hours. For red cinchona the first equivalent menstruum should contain 2.5% to 3.0% of hydrochloric acid, used in the same way.

[1] "The Function of Glycerin," JOUR. A. PH. A., 9, 868, 1920.

3. Hydrochloric acid, used in proper proportions, imparts stability to the preparation, reducing precipitation and holding the alkaloids in solution. This property is further aided by glycerin or sugars.

4. Lactic acid is inferior to hydrochloric acid in extracting cinchona.

5. Hot extraction is of no advantage for cinchona, and may be of disadvantage through the formation of phlobaphenes.

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THE QUANTITATIVE DETERMINATION OF SPARTEINE IN TABLETS.*

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This investigation was carried out with a view to developing a method for the quantitative determination of sparteine which would be rapid and simple and which could be depended upon to give accurate results.

This alkaloid was discovered in 1851 by Stenhouse,[1] who isolated it from *Spartium scoparium* Linné and later from the common Scotch Broom, *Cytisus scoparius* (Linné), Link, which now forms the chief source of supply. The alkaloid occurs in all parts of the plant and the amount present varies from 0.23% to 0.68%, being richest in March and poorest in August just after flowering.

Physical Properties.—Sparteine is a colorless oily liquid with a heavy odor recalling aniline, turning brown on exposure to air, especially if heated; readily soluble in alcohol, chloroform and ether, slightly soluble in water, and insoluble in benzine. Its density is greater than water, its specific gravity being 1.0196 at 20° C. It is laevo-rotatory. Its specific rotation in alcohol is variously given as —16.42°[2] and —14.6°.[3] The sulphate of the U. S. P. shows a rotation of — 22.12° in water.[2] The refractive index of the pure alkaloid is 1.5291 in sodium light at 20° C.[2] The boiling points given by various authors are: 328° C.,[3] 288° C.,[6] 311° C.,[7] 326° C.[8] Under 18 mm. pressure it boils at 188° C., and at 754 mm. in hydrogen it boils at 325° C.[2] It is slightly volatile at 100° C., if the heat is applied for a considerable length of time as is shown by an experiment described later in this paper. H. W. Jones[4] states that in the quantitative determination heat must be avoided, but gives no reason for this observation.

Chemical Properties.—Sparteine has the formula $C_{15}H_{26}N_2$, mol. wt. 234.30, and the sulphate of the U. S. P. is $C_{15}H_{26}N_2H_2SO_4.5H_2O$, mol. wt. 422.39. A number of attempts have been made to determine the structure of this alkaloid, perhaps the most comprehensive of which is that by Moureau and Valeur;[11] but so far its structure has not been established. It is readily oxidized, giving a great variety of oxidation products, none of which have, however, thrown much light on the structure of the alkaloid. The brown color observed when sparteine is heated in air is probably due to a partial oxidation. According to the British Pharmaceutical Codex, sparteine absorbs oxygen under the influence of air and light, becoming yellowish to dark brown and thicker.

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