Let us as pharmacognosists prepare now to show the students the way in which to apply the knowledge as obtained in Pharmacognosy and Materia Medica, besides holding them for a grade in the final examination. May I ask, "Are you teaching the correct interpretation of the Digitalis-Therapy Problem or are you merely having your students prepare elaborate drawings of the glandular and non-glandular hairs on the mid rib and leaf of this plant? Do you merely teach the students the names of the glucosides present, from the angle of the textbook, or do you teach same from the angle of the Digitalis-Therapy Problem?

Do we as pharmacognosists embody the thought in our teaching as has been expressed by Glenn Frank, President of Wisconsin University, as follows:

"I should like to see an educational experiment made in which a good daily newspaper was the only textbook used, with widely informed and alert-minded teachers simply reading over the newspaper with the students, and trying each day to induce the students to fill in the background and to find the meaning of the news. I venture that in four years or less we could produce a more thoroughly educated and more broadly informed type of graduate than by the more or less helter-skelter process of an extreme elective system under which the student may learn a great deal about a great many things without ever relating his knowledge to current human affairs or even seeing present-day society."

In the "daily newspaper" of your Pharmacognosy class, do your students merely read the paper, without filling in the background or relating the information as thus secured to the problems of future life as retail pharmacists?

We have seen Pharmacognosy of the past—we are now experiencing Pharmacognosy of the present—but what of Pharmacognosy of the future? That is your problem—that is my problem—that which I have set forth in this paper partly explains some thoughts that I have in mind as to how I am trying to meet up with Pharmacognosy of the present and the future, in which day by day the student is being shown the why and the wherefore as well as the relation of same to the future problems that are bound to arise for pharmacists of to-morrow.

NEW METHODS FOR THE DETERMINATION OF CINCHOPHEN AND THE CHOICE OF INDICATORS FOR ITS TITRATION.*

BY S. PALKIN.

Previously described methods[1,2] for the determination of cinchophen (2 phenylcinchoninic acid) in medicinal preparations depend on the extraction of the dry powdered material with hot alcohol or similar solvent and titration with standard alkali.

The sparing solubility of crystalline cinchophen in organic solvents in general and in solvents immiscible with water in particular has apparently led to the erroneous conclusion that quantitative extraction from aqueous medium cannot be accomplished.

Although it behaves like a fairly strong acid, forming stable salts with alkalies, cinchophen exhibits only weakly basic properties in aqueous solution. These

* Presented before the Section of Chemistry of Medicinal Products at the Richmond meeting, April 1927.

[1] Rabak, "Ann. Reports, Chem. Lab. Am. Med. Assoc.," 11, 73 (1918).

[2] Rabak, *J. Assoc. Offic. Agri. Chem.*, 7, 32 (1923); THIS JOURNAL, 16, 15 (1927).

basic properties are so weak that cinchophen can be removed completely from aqueous solution by extraction with ether or chloroform, even in the presence of an excess of acid. Quantitative Method No. 1 depends on this.

Another gravimetric method (Method 2) depends on the conversion of cinchophen to a "perbromide." This bromine addition compound is insoluble in aqueous acid medium, and in a freshly precipitated form it can readily be extracted with ether. On evaporation of the solvent and on heating, most of the additive bromine of addition is removed, leaving the cinchophen essentially in the form of the hydrobromide. The remaining bromine may be removed by chemical means. Hydrogen halide compounds of cinchophen, particularly the hydrochloride, have been described.[1]

TITRATION OF CINCHOPHEN.

The usual procedure for titrating cinchophen[2] consists in dissolving it in neutral alcohol and titrating directly with standard alkali, using phenolphthalein as an indicator. Experiments with the titration of cinchophen (in the absence of alcohol) by dissolving the compound in an excess of standard alkali and titrating back with acid to phenolphthalein gave values too high by 1 to 2%. p_H determinations of the aqueous solution of the neutral salt of cinchophen by the indicator method showed that the hydrogen-ion value in water solution was about 7.5 to 7.6, and by the hydrogen electrode[3] 7.38. The salt used was prepared by combining exact molecular quantities of pure cinchophen with hydrochloric acid. Electrometric titrations were made, using quinhydrone and calomel electrodes as described by Rasmoussen and Schou[4] and by Wales,[5] by dissolving pure cinchophen in an excess of acid and titrating back with alkali. Hydrogen-ion values thus obtained for the region of most rapid voltage change were 6.5 to 8.5 (mid-point 7.5). As the p_H range of phenolphthalein is 8.3 to 10,[6] it would appear that this is not the correct indicator for titrating this compound in aqueous solution and that the following indicators would more closely fit the p_H value of the neutral salt: cresol red (p_H 7.2–8.8),[6] phenol red (p_H 6.8–8.4),[5] bromthymol blue (p_H 6–7.6).[6]

METHOD 1. EXTRACTION OF CINCHOPHEN FROM AQUEOUS MEDIUM.

The alkaline solution of the cinchophen (not over 0.3 or 0.4 of a Gm. in about 50 cc.) is acidified with dilute sulphuric acid, so that an excess to the extent of about 10 or 15 cc. of 2 *N* acid is present. This mixture is shaken out with an equal volume of a previously prepared mixture of chloroform and ether (1:1). The chloroform-ether layer is then drawn off into another separatory funnel and the first funnel is washed with a little solvent to remove any of the extract from the stem of the funnel. The chloroform-ether extract is then washed with 15 to 20 cc. of water and the solvent mixture drawn off into a third separatory funnel and given a similar washing and the same precautions as regards complete transfer,

[1] "New and Nonofficial Remedies," p. 116 (1926).

[2] Rabak, *loc. cit.* (1).

[3] Waterman electrode vessel used. Design not yet published.

[4] *Pharm. Zentralhalle*, 65, 729 (1924).

[5] *Ind. Eng. Chem.*, 18, 390 (1925).

[6] Clark, "The Determination of Hydrogen Ions," p. 78 (1925).

etc., are taken in this case. The extract is then drawn off into a tared 100- or 150-cc. Erlenmeyer flask and evaporated on the steam-bath, preferably with air blast. Two or three more such extractions are made taking all the precautions of washing the extract, etc., as described in the first extraction and all the extracts added to the original. The combined extracts on evaporation to dryness are then taken up in a little absolute alcohol and evaporated to dryness carefully in order to avoid possible decrepitation. When evaporated to dryness the flask and contents are put in an oven and dried at 100 for one-half hour or more until constant weight is obtained.

METHOD 2. DETERMINATION OF CINCHOPHEN AS THE HYDROBROMIDE.

A bromide-bromate solution is prepared by dissolving 6 Gm. of potassium bromate and 100 Gm. of potassium bromide in 500 cc. of water. To the alkaline solution of the cinchophen in a volume of about 25 cc. containing not exceeding 200 mg. there is added a slight excess of dilute sulphuric acid, about 10 cc. of 2 *N* sulphuric acid for each 100 mg. of the compound. The slight precipitate of phenylcinchoninic acid first formed should redissolve when the acid has all been added. To this is then added about 10 cc. of the bromide-bromate solution for each 100 mg. of the compound, the whole rotated slightly and allowed to stand 5 or 10 minutes. The whole is then transferred to a 200-cc. separatory funnel and extracted three or four times with ether, using at least an equal volume of ether for each of the first two extractions. It has been found convenient to conduct the extraction in the following manner:

The aqueous layer is drawn off from the first funnel into a vessel such as a beaker or flask and the ethereal extract given a preliminary washing with about 5 cc. of water, more particularly to wash the stem of the funnel. The ethereal extract is then drawn into a second funnel where it is given a washing with about 25 or 30 cc. of water. This is drawn off into a second vessel and the ether extract again washed with a small quantity of water and finally the ether is drawn into a tared Erlenmeyer flask of about 150-cc. capacity taking the usual precautions of complete transfer, washing the funnel stem with ether, etc. In this manner it becomes unnecessary to filter the ether extract as all salts and acid will have been completely removed by the washing. This process of extraction is repeated two or three times, washed, etc., as provided in the first extraction and the combined ether extracts evaporated carefully on the steam-bath to low volume. Care must be taken at this point not to let the residue go to dryness as this compound under those conditions decrepitates violently. The major portion of bromine will have been volatilized during evaporation. In order to remove the remainder of bromine, several treatments with acetone are given to convert the bromine to brom-acetone. This is more readily removed than the bromine itself. For this purpose there are added about 5 cc. of acetone and the mixture evaporated nearly to dryness. The residue is then taken up in another 5 or 10 cc. of acetone. When all has gone into solution it is evaporated to dryness using air blast and this process of reëvaporation of the acetone solution is repeated several times *until there are no longer perceptible fumes of brom-acetone* when the product has gone to dryness. This residue is then dried in the oven for one-half hour or longer to a constant weight at a temperature of 100° to 110° C. The factor for converting the hydrobromide deriv-

ative of cinchophen to the original cinchophen is 0.754. If desired this compound can then be reconverted to cinchophen by treatment with alkali and extracted as directed in Method 1.

TABLE I.—RESULTS OBTAINED BY USING METHODS 1 AND 2.

Method.	Quantity of pure cinchophen taken. Mg.	Quantity of hydrobromide obtained.	Quantity of cinchophen recovered. Mg.
1	100		95.5
			100.0
			99.7
1	200		
			200.2
			200.5
1	500		
			498.3
			498.5
2	100	132.8	101.1
		132.2	99.7
		132.0	99.5
2	200	263.8	198.9
2	500	660.5	498.6

SUMMARY.

Two new methods for the quantitative determination of cinchophen are described. One depends on the extraction of cinchophen as such from an acid solution with an immiscible solvent; the other depends on the conversion of cinchophen to a bromine addition compound of its hydrobromide, which is extracted with ether and determined as the hydrobromide. Data showing results obtained by the respective methods are given.

Determinations by electrometric and indicator methods show that phenol red, brom-thymol blue and cresol red are suitable indicators for the titration of cinchophen.

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FURTHER STUDIES ON THE PHYSIOLOGIC ACTION OF PROPYLENE.*

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At the Buffalo (August 1924) meeting of this association one of us (1) presented a preliminary report of studies on the physiologic action of several hydrocarbons of the olefine series. A later communication (2) reported further studies on the physiologic action of unsaturated hydrocarbons of the acetylene and diene series. Other papers by Riggs and Goulden (3), Halsey and his co-workers (4) and (5) and by Brown (6) reported more detailed studies on the physiologic action of propylene, the only one of the series of hydrocarbons studied, which gave promise of being of any practical value as an anesthetic. It should in this connection be remembered that one of the olefine hydrocarbons ethylene, had pre-

* Scientific Section, A. PH. A., Philadelphia meeting, 1926.