Hypochlorite solutions used for disinfecting water supplies, bathing tanks, streets, and in laundries to destroy microörganisms and to remove stains, are made on a large scale by the electrolytic process. A 4 per cent. solution of sodium chloride in water when treated with 10 amperes direct current at 220 volts, can produce twelve gallons of sodium hypochlorite solution of 2 per cent. strength in one hour. (For references see list following No. 3.)

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(To be continued.)

THE UNITED STATES PHARMACOPŒIA FROM THE STANDPOINT OF THE ANALYST.*

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Before the Food and Drugs Act was passed, in 1906, the Pharmacopœia did not so seriously engage the attention of drug analysts as it has since. Previous to that time it is true that those who were engaged in the production of substances described in the Pharmacopœia were in honor bound to insure that such products conformed in purity to the standards prescribed by the U. S. P., but the analyst was not held to the U. S. P. methods of analysis so long as he was confident that the methods of his own selection were as accurate as those of the Pharmacopœia. However, with the coming of the Food and Drugs Act, added responsibilities were placed on the Pharmacopœia. The regulations for the enforcement of the Food and Drugs Act prescribe that the methods of analysis given in the Pharmacopœia or the National Formulary shall be used in the analysis of all drugs for which the United States Pharmacopœia or the National Formulary describes methods. In this the federal officials have no choice unless it can be shown to the satisfaction of the trial courts that a particular method described in the U. S. P. or N. F. is faulty. Many states and municipalities also have adopted the Pharmacopœia as a standard in the enforcement of their drug laws.

For more than 20 years I have been engaged in the analysis of medicines and in preparing standards for them. During this time I have made use of the seventh, eighth and ninth revisions of the Pharmacopœia. In the earlier editions there were fewer substances (other than the vegetable drugs) for which assays were prescribed than obtain to-day. As the work became of greater and greater importance from a legal standpoint, the number of substances standardized by assay has markedly increased until in the issue now official there are no less than 277 substances for which a quantitative assay is provided. In a few cases an assay is provided for more than one constituent in a preparation. Examples are: Compound solution of iodine which assays the free iodine and the potassium iodide; the same is true for tincture of iodine compound; also for oil of bitter almond which determines the hydrocyanic acid and the benzaldehyde. In the enumeration mentioned the double assay is counted only as one. In addition to the quantitative assay for the chief constituent of many substances, the Pharmacopœia requires the determina-

* Read before Chicago Branch, A. Ph. A., January meeting, 1924.

tion of many constants such as specific gravity, the saponification numbers and the iodine numbers of numerous fats and oils.

In general, the analytical methods of the Pharmacopœia are reasonably satisfactory. There have been numerous criticisms of some of them, but I understand that most of the objectionable features are to be remedied in the forthcoming revision. However, there are still some minor faults which require modification before the book becomes irreproachable. I shall discuss a few of these in the hope that some of the suggestions may be of use to the Committee of Revision. Consequently I trust that I shall be pardoned if some of the criticisms offered have already been considered by this Committee.

OPTICAL PROPERTIES.

Birotatory Properties of Lactose.

The Pharmacopœia describes methods for determining the specific rotatory power of a number of organic substances such as volatile oils and the sugars, but it does not mention that certain sugars possess the property of what is known as birotation, *i. e.*, a change in the optical activity of the sugar solution on standing. The specific rotatory power of lactose is given in the textual description of that substance in the Pharmacopœia, but no mention is made of its birotatory peculiarities. Because of this omission, very serious errors might be obtained in the results by analysts. In the lactose description, directions should be given for overcoming the birotatory effects either by allowing the solution to stand over night or by adding a few drops of ammonia water before the solution is made up to volume.

Specific Rotatory Power of Alkaloids.

At present the specific rotatory values for alkaloids and their salts are not given although, if optically active, the statement is generally made that the alkaloid has optical properties. Since the specific rotatory power is a constant, it should be given for every optically active alkaloid and alkaloidal salt which is described in the Pharmacopœia. Such information would be of great value in establishing the purity of alkaloids in laboratory control. This information, or the most of it, is already in the literature, so that but little research would be necessary to make the changes. The value of the polariscope in the study of alkaloids has been emphasized by Murray[1] and by Eaton.[2]

Index of Refraction.

The index of refraction is an important factor in the analysis of oils and fats. What has been said about the value of the optical rotation applies with almost equal force to the importance of the indices of refraction. This constant should be stated much more frequently in the Pharmacopœia than it is.

SOLUBILITIES OF ORGANIC SUBSTANCES.

Petroleum Benzin.

The solubility of organic substances in petroleum benzin is not stated so frequently as it should be. There are several substances described in the Pharma-

[1] A. G. Murray, JOUR. A. PH. A., 10, 736, 1921.

[2] E. O. Eaton, *Jour. A. O. A. C.*, 5, 594, 1922.

copœia which are insoluble in petroleum benzin, but which are soluble in other organic solvents such as alcohol, chloroform and ether. For example, acetphenetidin is insoluble while amidopyrine is quite soluble. Cocaine is soluble and quinine is almost insoluble. These differences in solubility suggest methods for the separation of the individuals in either couple when in mixture. Another example is phenolphthalein which is insoluble in petroleum benzin; fats, such as those from chocolate are soluble. This feature is often employed in the analysis of phenolphthalein tablets containing chocolate—the fat is removed by petroleum benzin after which the phenolphthalein is removed by acetone, and still later the sugar, if present, by water. If the Pharmacopœia would state the solubility of such substances in petroleum benzin methods for the separation of many substances in mixtures would be suggested. It is true that this would require some research, as all of the needed information is not in the literature at present.

Benzol.

What has been stated about the desirability of more information concerning the solubility of organic substances in petroleum benzin applies with almost equal force to benzol. For example, caffeine is readily soluble in benzol, while theobromine requires 100,000 parts of the solvent for solution. A method for the separation of these alkaloids by means of this solvent is mentioned in the literature[3] yet the Pharmacopœia makes no statement about the solubility of caffeine in benzol. Likewise, morphine is insoluble in benzol as stated by the U. S. P., but the fact that codeine is soluble is not stated. In the manufacture of alkaloids from opium, this property is employed to advantage.

Color Reactions.

The Pharmacopœia does not give as many color reactions as it should. For example, the Pharmacopœia states that salicin gives a red color with sulphuric acid which disappears on the addition of water. Phenolphthalein gives a similar reaction but this is not mentioned. Many other substances give red colors with sulphuric acid such as thebaine, one of the opium alkaloids, and saligenin, so that the reaction with salicin is not characteristic.

Methyl Orange as an Indicator.

The Pharmacopœia still directs the use of methyl orange as an indicator in certain titrations. This is a procedure scarcely warranted. Critical analysts of to-day do not consider methyl orange a good indicator since there are others so much more sensitive and reliable. For example, in the titration of free ammonia the Pharmacopœia permits the use either of methyl orange or of litmus. Most analysts use alizarin red in titrating ammonia as this is much sharper in reaction than either litmus or methyl orange.

Solubilities of the Hydrochlorides of the Alkaloids in Chloroform.

The hydrochlorides of many of the alkaloids are soluble in chloroform—a fact which is not sufficiently emphasized by the Pharmacopœia. In some cases the Pharmacopœia gives the information, in some it does not and in others the statements made are in error. For example, no statement of this property is made in the description of emetine hydrochloride, cotarnine hydrochloride or quinine and

[3] Henry, "The Plant Alkaloids," p. 317, 1913.

urea hydrochloride. The Pharmacopœia states that diacetyl morphine is soluble in chloroform, whereas the salt is very soluble. However, this is to be corrected in the forthcoming revision. Ethylmorphine hydrochloride is said to be only slightly soluble in chloroform, whereas it is very appreciably soluble. In the analytic determinations of alkaloids where chloroform is used as a solvent, if the solution be not sufficiently alkaline, some of the alkaloid will be shaken out as hydrochloride. This will render the findings too high if the residue be weighed, or too low if the alkaloid be titrated. It is obvious that these errors and omissions should be remedied.

Identity Tests.

Since the Pharmacopœia now has such an important forensic status, it is desirable that it should include as many tests for the identity of chemical substances as is consistent with space. At present the Pharmacopœia is very deficient in this particular. Characteristic tests should be given, if known, but if not, such tests should be substituted as will not react with impurities likely to be present, and a sufficient number of such tests should be given as to exclude other substances by elimination. At the minimum two tests as nearly characteristic as possible should be included for every organic chemical. I will cite a few examples: For many years the most satisfactory test for citric acid has been that of Denigé. This test, which depends on the precipitation of mercuric acetone-dicarboxylate, is sensitive in presence of tartaric acid and is both delicate and reliable. I understand that a modification of this test has been accepted for the forthcoming revision. This, together with the calcium precipitation test already official, will be amply sufficient to identify citric acid. However, for tartaric acid the Pharmacopœia still lacks a duplicate test, the present one being a precipitation reaction by potassium acetate. The most satisfactory test that I know of is as follows:

"If a drop of ferrous sulphate solution be added to a solution of tartaric acid or a soluble tartrate, a few drops of hydrogen peroxide solution added and the mixture finally treated with an excess of sodium hydroxide solution, a fine violet coloration is produced, which in strong solution of a tartrate, is so deep as to appear almost black. The test is sensitive in presence of citrates or citric acid."

This test is so satisfactory that it should be included in the Pharmacopœia.

Likewise the tests for morphine and its salts are insufficient in number. The two following tests as applied to morphine sulphate should be included:

If 0.01 Gm. of morphine sulphate be dissolved in 5 cc. of water and a few drops of tenth-normal iodine solution added to a portion of the solution a dense brown precipitate should be produced at once. Under the microscope the newly formed precipitate is seen to be amorphous but this soon crystallizes to dark red-brown plates, which are arranged in elongated aggregations. Many of the crystals have violet or red tints and a few exhibit prismatic colors (distinction from the *salts of other opium alkaloids*).

If about 0.1 Gm. of morphine sulphate be dissolved in 10 cc. of water, a few drops of a saturated, aqueous solution of iodic acid added, and the mixture shaken with 2 cc. of chloroform, the chloroform layer should be colored violet (distinction from the *salts of other opium alkaloids*).

In a similar way the tests for codeine and its salts are inadequate. The two following tests as applied to codeine phosphate might be included with advantage:

If about 0.01 Gm. of codeine phosphate be dissolved in 5 cc. of water, a few drops of potassium zinc iodide solution added, the mixture agitated and allowed to stand for some time, orange-

yellow, plate-like rosettes of crystals should be formed which under the microscope are seen to be composed of long interlaced needles, sometimes arranged in feather-duster shaped forms (distinction from the *salts of other opium alkaloids*).

If about 0.01 Gm. of codeine phosphate be dissolved in 1 cc. of water, a few drops of potassium sulphocyanate solution added and the solution shaken, a white, crystalline precipitate should be formed (distinction from the *salts of many other opium alkaloids*).

In the proposed text of the Tenth Revision as just published,[1] a description for benzocaine is given. In this it is noted that benzocaine gives a precipitate with iodine test solution. The precipitate which is given in the reaction has unique properties which render this test one of great value in the detection of benzocaine. I have found the following reaction to give good results:

To about 1 cc. of the solution of benzocaine (1: 100) in very dilute hydrochloric acid add about 1 cc. of iodine solution, shake the mixture and allow to stand for 10 minutes with occasional agitation. A reddish brown precipitate forms which changes to beautiful, lustrous scales. The crystals are best observed by agitating the test-tube in direct sunlight.

To the naked eye the precipitate reminds the observer of herapathite. Under the low power of the microscope the crystals appear as irregular aggregations of tables and prisms, most of which are brown; but many are brilliant yellow or brass colored; some are grass-green, others are blue or dark bluish violet and occasionally one is observed which exhibits prismatic colors. Combinations of two or more of these varieties are common.

Since this compound is so dissimilar to most others likely to be met with in the analysis of medicines, I submit the test to the Committee of Revision as worthy of description in the text of the Pharmacopœia.

I trust that these few examples of minor imperfections in the Pharmacopœia will be sufficient to indicate that the analytical methods should be studied more critically in their minute details. The Association of Official Agricultural Chemists through its referees is constantly at work in perfecting analytical methods for substances not in the Pharmacopœia. As a result the methods adopted by the A. O. A. C. have an enviable reputation among chemists both here and abroad and have received cordial recognition by the courts. The Committee of Revision of the U. S. P. would do well to follow a similar plan of continuous revision. A critical study of the analytical methods of the Pharmacopœia could well occupy the entire time of an expert analyst.

SUMMARY.

From the standpoint of the analyst the Pharmacopœia is indispensable. It is particularly important to those engaged in the enforcement of drug laws and to those who manufacture drug products. In order to hold its prestige before the courts the Pharmacopœia should contain tests sufficient in number and reliability to identify every substance described in the text and to establish the degree of purity required for such substances. The Pharmacopœia now official is deficient in these requirements in several minor particulars although it is superior to any of its predecessors. The proposed text for the next revision so far as published is still deficient. The Pharmacopœia is not likely to become a satisfactory standard for the analyst until the plan of continuous revision is adopted by the Committee of Revision.

[1] JOUR. A. PH. A., 12, 1107, 1922.