NOTES ON CHEMICAL TESTS OF THE UNITED STATES PHARMACOPŒIA.*

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SPECIAL METHODS.

ACETANILIDUM.—The melting points of good products may range between 112° and 115°. Chemical authorities give figures varying from 112° to 116° for the pure substance. A boiling point determination is not required as a test of purity. The U. S. P. requirements regarding inorganic impurities are somewhat vague; foreign pharmcopœias allow limits of 0.05 to 0.1 per cent; products containing not more than 0.05 per cent. of non-volatile matter are readily obtainable.

ACETONUM.—The tests and physical constants given cannot be entirely relied upon to determine if a given sample contain the required percentage of absolute acetone, because of the probable presence of small amounts of methyl alcohol. Messinger's method is generally regarded to be the most reliable for an assay, although it includes any "acetone oils" that may be present also, but these, when present in considerable quantity, are detected by a raised boiling point. The details may be conveniently carried out as follows: About 2 gm. of acetone are weighed in a stoppered weighing-bottle containing about 10 cc. of water, then diluted with water to 1 liter. Of this solution, 20 cc. are mixed with 25 cc. of n/1 sodium hydroxide in a 250 cc. glass-stoppered flask, 50 cc. of n/10 iodine added, and the mixture allowed to stand 15 minutes. It is then acidulated with about 25 cc. of n/1 hydrochloric acid and the liberated excess of iodine titrated with n/10 sodium thiosulphate. Each cc. of n/10 iodine (O=16) consumed in the formation of iodoform corresponds to 0.0009675 gm. of acetone. A blank test should be made with the reagents and any iodine consumed deducted from that consumed in the determination. The U. S. P. boiling point applies to normal barometric pressure only. Since glass loses weight during contact with steam and hot water, platinum and well-glazed porcelain dishes are preferable for determining the non-volatile matter.

ACETPHENETIDINUM.—A melting point interval of 134° to 135° is slightly narrow, as satisfactory products often begin to melt at about 133°. Non-volatile matter should not exceed 0.05 per cent. In the bromine test for acetanilide, the bromine water should be added drop by drop, with agitation after each addition, until the solution is permanently yellow. In case a considerable amount of bromine water is added all at once, a turbidity or precipitate is liable to form with pure acetphenetidin. The second test for acetanilide is superfluous; it has been found faulty and misleading by various analysts. The test for para-phenetidin may fail to show presence of traces of this unless a control test is made with a sample of known purity and the resulting colors compared. The delicacy of the test may be increased by boiling 1 gm. of acetphenetidin, 3 cc. of

alcohol, and 10 cc. of water with one drop of n/10 iodine, when the rose tint produced by minute traces of paraphenetidin will be brought out more distinctly. Pure acetphenetidin has a slightly bitter taste; the U. S. P. and other authorities state that it is tasteless.

ACIDUM ACETICUM.—If non-volatile matter is determined after supersaturation with ammonia water, as officially directed, allowance should be made for non-volatile impurities in the latter, as they are always present to some extent in ammonia that has been kept in glass containers. It seems preferable to evaporate the acid without previous neutralization. The accuracy of the permanganate test can be increased by measuring the reagent from a 1 cc. pipette instead of dropping it, assuming a drop to be equal to 0.05 cc., also by at least doubling all the quantities. Arsenic is considered by various authorities a probable impurity; it may be detected by the official Gutzeit test.

ACIDUM ACETICUM DILITUM.—Diluted acids are required (see *"Introductory Notices"* of the U. S. P., p. LVII) to be brought to the strength of the stronger acid before application of the tests given for the stronger acid, or a proportionately larger quantity of the weaker is to be taken for each test. The acid is too weak for direct application of the test for formic and sulphurous acids and concentration before testing is likely to eliminate these volatile impurities, therefore it seems best to supersaturate it with a fixed alkali, then evaporate to the required volume, before making the test.

ACIDUM ACETICUM GLACIALE.—A boiling point determination is not necessary to establish purity and strength. A congealing point determination gives the strength of acids above 95 per cent. at least as accurately as a titration, in shorter time and with less labor. According to Ruedorf, acetic acid containing 0.98 per cent. of water congeals at 14.8°; that containing 0.497 per cent., at 15.65°; the absolute acid at 16.7°. The titration is more conveniently made with 2 to 2.5 cc. of the acid, as 3 cc. require more than 50 cc. of normal alkali.

ACIDUM BENZOICUM.—While the U. S. P. includes both the synthetic and the natural acid in its descriptions and tests, these do not distinguish one from the other, except in the statement that the acid sublimed from benzoin is more soluble in water and has a lower melting point than that made by *toluol*. But, as·will be shown later, this is not a satisfactory means of differentiation, while those who purchase natural acid at a cost three times that of the synthetic, are entitled to what they pay for. In chemical literature no method is to be found that will afford a sure means of detecting adulteration or substitution, but if it can safely be assumed, what is generally conceded to be true, that natural benzoic acid never contains chlorine in organic combination, this fact can be utilized, since no artificial acid free from chlorobenzoic acid has, up to the present time, been placed on the market at a cost low enough to make substitution and adulteration worth while. . If, then, no chlorine is found in a sample when tested by the official method, with chlorine-free calcium carbonate, it may be considered that its source was benzoin, solely, natural acid made from hippuric acid no longer being an article of commerce. Unfortunately the natural acid of the market nearly always contains traces of hydrochloric acid or metallic chlorides, and this fact has heretofore been considered to bar this means of differentiation. Simple as it seems,

the writer has not been able to find, in the literature treating of this subject, the suggestion to test for *organic* chlorine in presence of the *inorganic* chlorine. This may be done by quantitative determinations of total chlorine and of inorganic chlorine in separate portions of a sample. About 5 gm. or more, after conversion into the calcium salt with an excess of pure calcium carbonate and a little water, should be charred in a platinum dish at a low red heat, the residue extracted with boiling water, dried, and incinerated at a low temperature. The ash should also be extracted with boiling water. The total chlorine may then be determined in the combined filtered solutions, preferably by Volhard's method. Another portion of the sample may be dissolved in weak ammonia water (free from chloride), nitric acid added until no further precipitation takes place, and inorganic chlorine determined in the filtrate by the same method. The second result subtracted from the first, gives the organic chlorine, of which synthetic benzoic acid usually contains 0.05 per cent. or more. If the two results are the same, organic chlorine is absent, and the sample may be considered free from adulteration with synthetic acid. For accurate determinations Volhard's method requires that the silver chloride be removed by filtration before titrating the excess of silver and where such small quantities of chlorine are involved, it is important that the n/10 silver nitrate should not be more than 0.2 cc. in excess, according to A. T. Stuart (Jour. Am. Chem. Soc., 1911, v. 33, p. 1344). Benzoic acid from benzoin, as now found on the market, contains less of its characteristic impurities than formerly and sometimes scarcely differs in solubility and melting point from the artificial acid. The principal difference between the best grades of the two kinds, in addition to those already mentioned, are as follows: The synthetic acid is white, in thin, lustrous scales, and has an odor of benzaldehyde; the natural acid is yellowish-white, in small, friable acicular crystals, and has an odor of benzoin, quite different from that of benzaldehyde. A solution of about 0.5 gm. of the first in 10 cc. of sulphuric acid should not be darker than yellow at 50°; the second may produce a light brown solution under similar conditions. Both kinds should not contain more than 0.05 per cent. of non-volatile matter.

ACIDUM BORICUM.—In the identity test with turmeric paper, ammonia changes the color to greenish-black, not bluish-black, as stated. The test for arsenic, as now given, permits presence of at least 20 parts per million, which seems rather too much, when it is considered that many other substances, given in smaller doses, are limited to 10 parts per million. Glycerin used for the titration should be neutralized, as otherwise the result will be a little too high. All available glycerin has an acid reaction. The quantity of boric acid directed for the titration is hardly sufficient for accurate work; about 2.5 gm. would be preferable, but care should be taken that the liquid contains at least 30 per cent. of glycerin at the end of the titration, which, according to R. T. Thompson, is necessary for correct results. It may be said, however, that a titration is not necessary to determine the purity of boric acid. If it stands the other U. S. P. tests, it cannot well contain more than 0.2 per cent. of impurities.

ACIDUM CAMPHORICUM.—It should not yield more than 0.05 per cent. of residue on incineration. The melting point has been found to vary from 183° to 187°. The Brit. Pharm. Codex considers 180° the lowest that may be permitted.

ACIDUM CITRICUM.—The U. S. P. gives no tests for tartaric and oxalic acids, unless the lime water identity test be so considered. A test for tartaric acid used by a number of foreign pharmacopœias and which has been found satisfactory, is made by mixing about 0.5 gm. of the acid with 5 cc. of sulphuric acid in a porcelain dish and heating for 15 minutes on a water-bath, protecting the contents of the dish from dust meanwhile. No color darker than yellow should develop. In presence of tartaric acid the liquid becomes brown to black. Oxalic acid is best detected by the test given in the U. S. P. for oxalic in tartaric acid. Arsenic is recognized as a probable impurity by several foreign pharmacopœias. Excessive amounts can be detected by the official Gutzeit test.

ACIDUM GALLICUM.—It is not soluble in 40 parts of ether, as stated in the U. S. P. and various other authorities. A. Seidell found it soluble in 72 parts of absolute ether at 25°. A limit of 0.1 per cent. of ash must be permitted. A melting point determination is useless as a test of purity, owing to decomposition near the melting temperature.

ACIDUM HYDRIODICUM DILUTUM.—The specific gravity in the U. S. P. applies only to products made by the official method, containing a large amount of potassium bitartrate. A purer acid of the same strength has a considerably lower specific gravity. For the titration with silver nitrate, the acid should be diluted with at least twice as much water as is directed, to prevent reduction of silver by the hypophosphite present. A glass-stoppered flask should be used. No test is provided for hydrochloric and hydrobromic acids, which may be fraudulently added. For their detection a test may be based on the same principle as is used in the U. S. P. test for hydrochloric in hydrobromic acid, substituting ammonia water for ammonium carbonate. The presence of traces of hydrochloric acid, however, cannot always be avoided in a carefully made product.

ACIDUM HYDROBROMICUM DILUTUM.—The requirement that no "appreciable" residue should remain after evaporation of 10 cc., is subject to differences of interpretation; a well made product should not leave more than 0.01 per cent. A treatment with sulphurous and sulphuric acids, as a preparation for the test for arsenic is neither necessary nor desirable, as the arsenic is likely to be volatilized in the process. Volhard's method is more convenient than Mohr's for an assay and just as accurate.

ACIDUM HYDROCHLORICUM.—It should not contain more than 0.01 per cent. of non-volatile matter. The preliminary treatment for the arsenic test should be omitted, as the arsenic would be volatilized as arsenous chloride. The U. S. P. test for free chlorine is not conclusive, as ferric chloride, present in permissible quantity, may liberate iodine under the conditions of the test.

ACIDUM HYDROCYANICUM.—It is not "completely" volatilized by heat, but should not leave more than 0.01 per cent. of residue.

Acidum Hypophosphorosum.—Products containing much oxalic acid and calcium oxalate have been found in this market during recent years by E. L. Patch, E. H. Gane, and others. The U. S. P. has no test for this dangerous contamination, the entire absence of which should be demanded. The detection of oxalates may be slightly complicated by the presence of phosphoric, phosphorous, sulphuric, or tartaric acid; a precipitate obtained by the addition of calcium chloride

and an excess of ammonia may consist of the calcium salts of any of these, but if this be found readily soluble in acetic acid, absence of oxalic acid may be assumed; any portion of it not readily soluble should be further examined according to the rules given in any text book on Qualitative Analysis. The official test for a limit of barium, another unnecessary and dangerous impurity, is inadequate, since phosphoric acid, which is always necessarily present to some extent,. precipitates barium phosphate, when an excess of ammonia is added. This is then filtered out, before the test for barium is made in the filtrate. As a substitute test the writer recommends that any precipitate, formed when the acid is nearly neutralized with ammonia water, potassium sulphate added, and the mixture allowed to stand several hours, should be required to be completely soluble in diluted hydrochloric acid, to show *absence* of barium.

Acidum Lacticum.—As has been pointed out in the journals by several authors, the concentrated acid of the market is a mixture of lactic acid and several lactic anhydrides. An acid having the specific gravity given by the U. S. P. contains from 72 to 75 per cent. of lactic acid and about 15 per cent. of anhydrides, which are convertible into lactic acid by contact with alkali or, more slowly and incompletely, by dilution with water. It is officially described as being colorless, but market products always have a slight yellowish tint. The ash limit is placed at 1 per cent., but products of good quality now do not yield more than 0.1 per cent. The official test for glycerin is unsatisfactory, because zinc lactate is taken up by alcohol together with any glycerin present and the taste of small quantities of the latter is masked thereby. The following test is used by various pharmacopœias and has been found more satisfactory: The concentrated acid is added drop by drop to ether of U. S. P. strength and the mixture shaken after addition of each drop. Neither a transient nor a permanent turbidity should result. When the acid contains about 2 per cent. of glycerin, a turbidity is produced after the addition of a few drops to 5 cc. of ether. When the addition of acid is continued, the turbidity finally disappears. Smaller quantities of glycerin can be detected when absolute ether is used. The U. S. P. gives no test for detection of additions such as tartaric, citric, oxalic, and phosphoric acids. A test given by most foreign pharmacopœias consists in heating the acid with an excess of lime water. No turbidity should be produced. Cold titration with alkali and phenolphthalein gives the actual lactic acid together with a small amount of anhydride, which is hydrated during the titration. Subsequent heating with an excess of alkali gives the remainder of anhydride. The assay may be carried out conveniently as follows: About 5 gm. of the sample are weighed in a stoppered weighing bottle, diluted with 50 cc. of water, and titrated with n/1 alkali until the entire solution becomes *momentarily* pink after mixing. The result is calculated as lactic acid. The solution is then heated for half an hour with 25 cc. more of n/1 alkali on a waterbath, cooled, and the excess of alkali determined with n/1 acid. The alkali consumed in the second titration represents the anhydrides, which are calculated in terms of lactic acid, for convenience. (See also E. Elvove, *Am. Jour. Phar.,* 1911, v. 83, p. 14.)

Acidum Nitricum.—It should not contain more than 0.01 per cent. of nonvolatile matter. A test for arsenic is unnecessary, as this is very improbable as an impurity; no other recognized authority gives a test for it. The official test, if

considered necessary, should be modified by evaporating the acid to dryness on a water-bath before the treatment with sulphuric and sulphurous acids. The official test for sulphuric acid does not prove "absence," but merely defines a limit.

Acidum Oleicum.—The specific gravity of products of U. S. P. standard may vary from 0.890 to 0.896 at 25°. It should not leave more than 0.1 per cent. of residue on incineration. The alcohol test for fixed oils has been shown by J. F. Woolsey and C. H. Ballinger to be incapable of detecting an admixture of 50 per cent. The official test for "undecomposed fat" in stearic acid can be recommended as a satisfactory substitute. It also shows presence of hydrocarbon oils. The lead test for limits of stearic and palmitic acids is too stringent for a product made by the official directions and is also defective in other respects. Since the limits of these acids are fixed by the congealing point, this test is superfluous. A test for free mineral acids, which may be present when the older methods of manufacture are used, might well be added. If the acid be shaken with an equal volume of water, the separated water should not be acid to methyl orange. Determinations of acid, saponification, and iodine values have been recommended, but seem unnecessary.

Acidum Phosphoricum.—While the U. S. P. allows 10 parts of arsenic per million, products containing less than half this amount are now readily obtained. The U. S. P. table of specific gravities and percentages has been found somewhat inaccurate and should not be relied upon for precise adjustments of strength. The official method of titration, as modified in 1907, has been found by J. Rosin to give results agreeing within 0.2 per cent. with the results obtained by gravimetric determination as magnesium pyrophosphate. It is necessary to adhere closely to the prescribed details regarding the ratio of sodium chloride and water to phosphoric acid for accurate results.

Acidum Salicylicum.—The natural acid of the market usually has a slight yellowish or pinkish tint and a slight odor, but the synthetic acid should be white and odorless. A melting interval of 156° to 157° is too narrow for the available product. G. A. Menge found the corrected melting intervals of 5 market samples to range from 157.5° to 158.9°. Natural acid, as found in commerce, is likely to give somewhat lower figures. An allowance of 0.6 per cent. of inorganic impurities is unnecessarily liberal; not more than 0.1 per cent. should be present. In the test for coloring matter a slight yellowish or pinkish tint must be allowed in the case of natural acid. All obtainable synthetic acid gives a yellow solution in sulphuric acid, when tested as officially directed; natural acid may produce a light brownish solution.

Acidum Stearicum.—The U. S. P. test for "undecomposed fat" also serves as a test for paraffin, which obviates the need of determining the acid or iodine value for detecting such admixture. Absence of free mineral acid may be established by shaking the melted acid with an equal volume of water, cooling, and testing the separated water with methyl orange.

Acidum Sulphuricum.—It should not contain more than 0.01 per cent. of non-volatile matter. When the acid is neutralized with ammonia water before volatilizing, as officially directed, the non-volatile matter derived from this should be deducted. It is preferable to evaporate without previous neutralization when a

hood having good draught is at hand. The quantity directed for titration is entirely too much; not much more than 1 cc. of concentrated acid should be taken.

Acidum Sulphuricum Aromaticum.—The time required for hydrolysis of the ethylsulphuric acid can be greatly shortened by heating with an excess of N/1 alkali.

Acidum Sulphurosum.—It is advisable to weigh the acid in a glass-stoppered flask large enough for the titration and containing enough water to prevent loss of sulphur dioxide by volatilization.

Acidum Tartaricum.—Arsenic is considered to be a possible contamination by some authorities. The U. S. P. Gutzeit test may be used for detecting excessive quantities.

Acidum Trichloraceticum.—The melting point may be expected to vary from the official figures (52°); the German Pharmacopœia gives 55°, the Swiss 56°. As this acid is extremely hygroscopic, a melting point determination with any degree of accuracy is impracticable. It should not leave more than 0.05 per cent. of residue on volatilization. The ferric chloride identity test should be omitted, as the pure acid gives no color. In addition to the U. S. P. tests, the ferrous sulphate test, made in the usual way, should not give a reaction for nitric acid and silver nitrate should show not more than slight traces of hydrochloric acid.

(To be continued.)

LISTER AND LISTERISM.

A man who leaves his name in his native language as the description of an art which has saved millions of lives in his lifetime is rare in human history, and such a man was Joseph Lister, the discoverer of the antiseptic system of treatment in surgery. He was the son of Joseph Jackson Lister, F. R. S., a distinguished microscopist and a member of the Society of Friends. His birthplace was Upton in Essex, and after his elementary education at Friends' schools he completed his classical and mathematical studies at University College, London, graduating as B. A. Lond. in 1847. He continued at the college as a medical student, and became M. B. Lond. and F. R. C. S. Eng. in 1852. After a short period at University College Hospital as a resident surgeon he visited Edinburgh, taking with him a letter from Professor Sharpey, then of world-wide reputation, to Professor Syme, who held the Surgery chair in the Edinburgh University, and the visit became a sojourn in Scotland of about a quarter of a century, during which he had discovered and perfected the antiseptic system of surgical treatment, filled the chairs of Surgery in Glasgow University (1860-69) and in Edinburgh University (1869-77), and became known throughout the civilized world as a distinguished surgeon and one of the greatest benefactors to humanity. In 1856 he married Agnes, the daughter of Professor Syme, and became an extra-mural lecturer in surgery of the Edinburgh Medical School, which he retained until his appointment to the Glasgow chair. He was a chemist and histologist of no mean ability, and was quick to appreciate the significance of Pasteur's work on fermentation, which led to the observation that that process and putrefaction are the result of microorganisms living upon the organic matter which ferments or putrefies. Hitherto