(61) "Vanilla;" John R. Jackson, *Am. J. Pharm.*, 317 (1875).
(62) "Vanilla;" Bentley & Trieman, "Medicinal Plants," 272 (1880).
(63) "Vanilla Pods, Method of Preserving," *Am. Druggist* (1892).
(64) "Vanilla, Relative Flavoring Value of True Vanilla Extract and Vanillin Solution;" F. M. Bayles, *Spice Mill*, 45, 1438.
(65) "The Vanilla Pod;" I. V. S. Stanislaus, *Tea and Coffee Trade Journal*, 42, 528, 674.
(66) "Conc. Vanilla Compounds;" Melvin DeGroote, *Spice Mill*, 45, 1042.
(67) "Vanilla Powders;" Melvin DeGroote, *Spice Mill*, 44, 312.
(68) "Tincture of Vanilla;" K. A. Bartlett, JOUR. A. PH. A., 9,706.
(69) "Tincture of Vanilla of NATIONAL FORMULARY;" *Ind. & Eng. Chem.*, 11, 953.
(70) "Vanilla Extract, The Analysis of;" Chas. H. LaWall and LeRoy Forman, JOUR. A. PH. A., 3, 258.
(71) "Vanilla Extract;" *Süddeut. Apoth.-Ztg.*, 51, 772.
(72) "Vanilla—Vanillin and Vanilla Extract;" W. L. Utermark, "Communication No. XVLI Trade Museum, No. 3 Collonial Institute of Amsterdam."
(73) "Suitability of Monel Metal* for Vanilla Flavoring Containers;" T. E. Hollingshead and T. J. Otterbacher, *Ind. Eng. Chem.*, 18, 871 (1926).

BROOKLYN RESEARCH LABORATORIES,
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A PHARMACEUTICAL STUDY OF SYRUP OF FERROUS IODIDE (1840–1927).

BY CATY J. BRAFORD AND H. A. LANGENHAN.

(*Continued from p. 437.*)

No. III. PRESERVATION OF SYRUP OF FERROUS IODIDE.

To find a satisfactory procedure for the preservation of **Liquor Ferri Iodidi** has been a problem with which the pharmacist has been working for a long time. As early as 1839 Frederking[1] suggested the use of saccharine material. The following year Proctor[2] published a paper in which he outlined the experiments he had performed with sugar of milk, manna, cane sugar, honey and "uncrystallizable" sugar. In 1841 Dupasquier[3] used "syrup of gum" to make his preparation more stable. Beral[4] added simple syrup. This experimentation probably led to the introduction of the **Syrupus Ferri Iodidi** into the U. S. P. of 1860.

Although the Syrup was more stable than the Liquor had been, the pharmacists still found it difficult to keep this preparation unchanged. Maisch[5] was an early worker who presented a theory of the decomposition. He considered that a solution of ferrous iodide was decomposed not only by light but also by the action of the atmospheric oxygen in the bottles that were only partly filled and frequently opened. He thought that the oxidation of the iron and liberation of iodine were hastened by the action of light. He found that when an altered solution was transferred to air-tight bottles, completely filled and exposed to direct sunlight, it resumed its transparency and the original color was completely, or at least par-

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* A non-corroding alloy of nickel, copper, cobalt and iron.—EDITOR.

[1] Frederking, *Am. J. Pharm.*, 58, 289 (1886).
[2] Procter, Wm., *Ibid.*, 12, 13 (1840).
[3] Dupasquier, *Jour. de Pharm.* (1841); through *Am. J. Pharm.*, 58, 289 (1886).
[4] Beral, *Am. J. Pharm.*, 13, 74 (1841), from *Jour. de Chem. Med.*
[5] Maisch, *Ibid.*, 27, 218 (1855).

tially, restored. Maisch concluded that after such a restoration the solution must be in some way altered and suggested that it would then contain some iodate of the "sesquioxide of iron."

The U. S. P. of 1860 directed that the Syrup be stored in "two-ounce, well-stopped" vials. The 1870 revision was about the same. These directions were modified in the next Pharmacopœia to read, "Transfer the contents (finished syrup) to small vials, which should be completely filled, securely corked and kept in a place accessible to daylight." In 1890 the directions were briefer, reading "small well stoppered and completely filled bottles." The U. S. P. of 1900 offered no method of preservation whatever but, in 1910, it was again specified that the syrup be kept in "completely filled, tightly stoppered bottles." The last Pharmacopœia offers the same method.

The belief that storing in a small bottle aided in the preservation of the syrup, because of lesser exposure to air, was evidently a common one. The Editor of the *American Journal of Pharmacy* published a note in 1868 in which he stated that he believed a "properly-made official syrup enclosed in small bottles (dry), closing them effectively and keeping it exposed to light, is the best protective method." Tilden[1] suggested layering the syrup with oil as a means of excluding the air and in that way preventing oxidation and decolorization. About the same time Hughes[2] published a paper on the subject of preservation in which he concluded that "a thick well-made syrup covered with parchment, kept in a warm place, keeps best." He especially condemned the practice of storing the syrup in cold dark cellars, and objected to the use of corks, due to the tannin that they might contain. The same year Holloway[3] recommended exposing the syrup to direct sunlight for a few hours daily so as to prevent oxidation. He also, like Maisch, stated that this process would restore a discolored preparation. Some years later Beck[4] devised a process for preservation in which "carbonic acid gas" was used to exclude all air. His article included an illustration of the apparatus which he had used to generate the carbon dioxide. Sawyer[5] suggested bottling the syrup in small vials while it was still hot, the size of the container to be varied according to the needs of the pharmacist. These vials were then to be sealed with a mixture of paraffin and white wax.

The various suggested methods for properly storing the syrup did not seem to overcome the difficulties of preservation, so other processes were adopted. These processes may be grouped into three classes. The first of these includes the introduction of sugar and its substitutes to the Liquor. The second deals with the introduction of both organic and inorganic acids and the salts of some of these. Group three is a collection of the miscellaneous processes which were suggested at different times.

No. 1.—Several sugars were used in the manufacture of the syrup. The U. S. P. preparation called for syrup made from sucrose, or cane sugar. Hammer[6]

[1] Tilden, *Pharm. Jour.*, 9, 260 (1867).
[2] Hughes, *Ibid.* (Nov. 1868); through *Am. J. Pharm.*, 41, 14 (1868).
[3] Holloway, *Ibid.*, 9, 471 (1867).
[4] Beck, *Am. J. Pharm.*, 64, 18 (1892).
[5] Sawyer, *Bull. Pharm.*, 23, 254 (1909).
[6] Hammer, *Pharmacist* (Apr. 1876); through "British Year Book of Pharm.," 287 (1876).

prepared a stable syrup in which he considered grape sugar to be the preservative. His theory was that "an aqueous solution of ferrous iodide is changed to free iodine and sesquioxide of iron, when it is partially acted upon by the oxygen of the air. Heat or direct sunlight will change the free iodine into hydriodic acid. Decomposition takes place if cane sugar is present in the diluted acid—the formation of grape sugar and the liberation of free iodine. The remaining portion of the uncombined cane sugar is at the same time exerting its action upon the precipitated oxide of iron, deoxidizing it and, thereby, increasing the percentage of grape sugar, the liberated iodine again combining with the deoxidized iron to form protoxide of iron. When this stage is reached it prevents further decomposition of the preparation and it may now be exposed to oxidizing influences, provided a certain percentage of grape sugar is present." Wayne[1] observed that grape sugar was sometimes deposited when a sample of the syrup was kept for some time and he considered such a change probably to be due to the conversion of cane sugar through the agency of the hydriodic acid present.

Cane sugar alone did not prove satisfactory and various experiments were made in which a portion of the saccharine substance was glucose. Interesting work along this line was presented by England,[2] who believed that if glucose would preserve Vallet's Mass it might prove efficient in the preservation of ferrous iodide. He first used the commercial glucose, and then a mixture of glucose and dextrin. These were too powerful in their actions; a large quantity would cause the precipitation of ferrous oxide and a small quantity allowed both oxidation and reduction. He next tried solid glucose and found it to be fairly satisfactory. He explained the decomposition of an unpreserved sample as first an oxidation to a ferric compound and then a precipitation of ferric hydrate and iodine. To the first reaction he gave the following equation: $2FeI_2 + O + H_2O \longrightarrow Fe_2I_2O_2 + 2HI$.

Glycerin[3] was suggested as a preservative for Syrup of Ferrous Iodide. Gregory[4] substituted it for the simple syrup. The investigations carried on by Wells[5] encountered the usual difficulties when the glycerin and syrup were mixed. To remedy this Wells used a glucose syrup. In 1900, Meredith[6] published a paper in which he discussed the question of whether or not glucose and glycerin really improve the keeping quality of the syrup. He concluded that glycerin is not objectionable medicinally; that it prevents oxidation and is thus a preservative; that it assimilates iodine after liberation, in a non-irritating form; and that it is not objectionable in this preparation. When it was to be used he recommended that it replace half of the sugar called for in the formula. Although he considered glycerin to be a good preservative, he thought that glucose was a better one, because it reduces iodine and forms hydriodic acid, and prevents oxidation. He found that a glucose solution having a specific gravity of 1.4 was the most efficient.

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[1] Wayne, "U. S. Disp.," ed., 13, 1433 (1875).

[2] England, *Am. J. Pharm.*, 60, 547 (1888).

[3] England, *Am. J. Pharm.*, 60, 547 (1888).

[4] Gregory, *New Rem.*, 110 (1878); through "British Year Book of Pharm.," 15, 329 (1878).

[5] Wells, "British Year Book of Pharm.," 21, 277 (1883); from *Pharm. J.*, 3rd series, 14, 82.

[6] Meredith, *Am. J. Pharm.*, 72, 468 (1900).

Other investigators[1,2] have worked with glucose and have obtained what they consider to be satisfactory results. A recent article[3] dealing with the "Relative Preservative Values of Glycerin and Sugar Solutions" offers the following conclusions in reference to Syrup of Ferrous Iodide:

1. Inversions and caramelization make sucrose solutions quite unsuited for preservatives.

2. Glycerin, on account of the opportunity of increasing the molarity, is more efficacious as a preservative.

Glucose was prescribed in the B. P. V formula, but according to Cowie[4] may not have been much of an improvement.

The above methods may have been successful but they were soon replaced by the second large group of preservatives, the acids and their salts.

No. 2.—As early as 1860, Ferdinand Mayer[5] published a paper on the Liquor Ferri Iodidi in which he recommended that Hyposulphite of Soda be used as a preservative, or as he called it, "a deoxidizing substance." His formula called for an excess of iodine to which the hyposulphite of soda was added in equivalent proportions, to form "hydriodic acid and tetrathionate of soda." He considered the salt to be inert but capable of insuring the permanency of the protoiodide.

Tschirner[6] suggested adding the sodium hyposulphite to the fresh syrup, rather than mixing it with the iodine and consequently decomposing it. The following year Judge[7] recommended that hypophosphorous acid be used in preference to sodium hyposulphite to restore Syrup of Ferrous Iodide. His theory was that sodium sulphate forms on the addition of sodium hyposulphite and that one-half of the sulphur precipitates, leaving the syrup as unpleasant in appearance as before the addition. Hypophosphorous acid having the same affinity for oxygen would effect the same change, leaving the syrup clear and of the proper color. Hausmann[8] conducted several experiments in view of preparing a more permanent syrup and his work showed that the addition of hypophosphorous acid was an aid in the preservation. Matuson[9] agreed with this and in his article published in 1903 he included a revised formula suggested by Robinson which called for the addition of twenty per cent acid. Hall[10] likewise added it.

The U. S. P. VIII and the U. S. P. IX directed that twenty cc. of diluted hypophosphorous be added to each one thousand cc. of Syrup of Ferrous Iodide. The last revision changed that slightly and prescribes five cc. of hypophosphorous acid, equivalent to fifteen cc. of the diluted acid, for each one thousand cc. of syrup.

Other acids and salts have been used and good results claimed. Groves[11] used

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[1] Lyon, *Pharm. J.*, 3rd series, 24, 863 (1894); through "British Year Book of Pharm.," 201 (1894).

[2] Pulsifer, *Pharm. Era*, 18, 489 (1897).

[3] Krantz, JOUR. A. PH. A., 12, 963 (1923).

[4] Cowie, *Pharm. J.*, 94, 236 (1914).

[5] Mayer, *Am. J. Pharm.*, 32, 175 (1860).

[6] Tschirner, *Am. J. Pharm.*, 47, 249 (1875).

[7] Judge, *Ibid.*, 48, 157 (1875).

[8] Hausmann, *Ibid.*, 72, 217 (1900).

[9] Matuson, *Ibid.*, 75, 71 (1903).

[10] Hall, *Bull. Pharm.*, 18, 374 (1904).

[11] Groves, *Pharm. J.*, 27, 421 (1868).

sulphuric and phosphoric acids. Rother[1] recommended the use of sodium sulphite, but specified that care be taken to add it after filtration as otherwise the sulphurous acid, which had been formed by the sodium sulphite reacting with the "iodohydric" acid, would be decomposed into free sulphur and water. Various other workers preferred tartaric acid.[2] The "French Codex" has prescribed its use also. Citric acid has been considered; experiments using it as a preservative have been carried on for a long time. As early as 1870 Beardsworth[3] found that bright light and citric acid would clarify a decolorized syrup and keep it clear. He recommended the addition of one grain of acid to each ounce of syrup. Parrish[4] also used it. A little later (1876) Dr. Pile[5] stated that he had been unsuccessful in preventing a change in Syrup of Ferrous Iodide by the addition of citric acid, unless the extra precaution were taken to keep the syrup in well-filled vials and excluded from contact with the air. The subject was discussed in foreign journals[6] and the addition of one and a half Gm. of acid to thirteen hundred Gm. of syrup was considered to be sufficient. In 1895, Girard[7] offered a new formula which he declared to be free from the objectionable features of the Pharmacopœial and the Codex formulas, *viz.:*

Iron	20 parts
Distilled water	100 parts

Proceed as directed under the Codex or Pharmacopœia and after the solution is obtained, mix it with the following syrup.

Citric acid	5 Gm.
Distilled water	100 Gm.
Alcoholic essence of orange peel	10 Gm.
Simple syrup q. s. (with the iron solution)	1 kilo

Cloughly[8] later suggested a new formula in which citric acid was one of the improvements. Various other workers[9,10,11,12,13] have from time to time suggested its use, varying the amount of acid from one-fourth to one per cent. Dr. Borisch[14] did considerable work on Syrup of Ferrous Iodide and he likewise suggested that it be preserved by the addition of citric acid (0.05%). Williams[15] reported that a more desirable syrup was furnished by the formula given in the Squibb's Labora-

[1] Rother, *Pharm. and Chem.*, 9, 193 (1876).

[2] Jeannel, *Bull. soc. pharm. Bordeaux*, through *Jour. Pharm.*, 41, 16 (1869).

[3] Beardsworth, "British Year Book of Pharm.," 7, 58 (1870).

[4] Parrish, *Am. J. Pharm.*, 48, 209 (1876).

[5] Pile, *Ibid.*, 48, 442 (1876).

[6] Carles, *Bull. Soc. Pharm. du Sud. Ouest*, through *Am. J. Pharm.*, 53, 359 (1881).

[7] Girard, *Pharm. Era*, 13, 334 (1895).

[8] Cloughly, "Proc. Mo. Pharm. Assoc.," 133, through A. PH. A. YEAR BOOK, 1, 65 (1912).

[9] Wiebelitz, *Pharm. Ztg. Berl.*, 51, 1004 (1906); through "Digest of Com." (1906).

[10] Lorenzen, *Apoth. Ztg.*, 23, 295 (1908); through "Digest of Com." (1908).

[11] Dunn, PROC. A. PH. A., 57, 950 (1909).

[12] Hommell, *Prac. Drug.*, 29, 29 (1911); through "Digest of Com." (1911).

[13] Caldwell, *Drug. Circ.* and *Chem. Gaz. N. Y.*, 49, 220 (1905); through "Digest of Com." (1905).

[14] Borisch, A. PH. A. YEAR BOOK, 2, 75 (1913); *Apoth. Ztg.*, 29, 902, through "Digest of Com." (1914).

[15] Williams, *Western Druggist*, 37, 6–7, through "Digest of Com." (1915).

tory notes in which citric acid was used. E. Fullerton Cook,[1] in an article discussing the Syrups and Elixirs of the U. S. P. IX and the N. F. IV, stated that citric acid was preferable to hypophosphorous acid. The next year another worker[2] suggested that it be used in the proportions of 0.05 to 0.1 grains to one hundred Gm. of syrup. Beringer[3] concluded from his observations that it has no reducing power on the sugar.

The pharmacopœias of Holland, Austria, Switzerland, Belgium and Hungary all prescribe the use of citric acid.

Potassium citrate[4,5] has been used during the last few years as a preservative and also as a means of obtaining a more palatable preparation.

Even hydriodic[6] and lactic[7] acids have been used. In each case the amount of acid was usually small, being between one-fourth and one per cent of the total volume.

No. 3.—The third group of preservatives includes the various other materials which have been suggested. Perhaps the most common of these is metallic iron, placed in the finished syrup. In this way any free hydrogen iodide was converted to ferrous iodide before it could decompose and liberate free iodine. According to England[7] this did not retard the ultimate decomposition as "it seems plain that it did not prevent the formation of the ferric oxysalt and hydriodic acid but merely preserved for a time the transparent color of the syrup."

Izard[8] added a few drops of alcohol as soon as the iodine had been combined with the iron. He worked on the theory that an aldehyde would be formed and would prevent the oxidation of the ferrous salt. Another worker[9] added one per cent of alcohol to the finished preparation.

Although preservatives evidently have been accepted as being essential, and have been adopted by the U. S. P. and other pharmacopœias, one still finds workers who consider them not only unnecessary but even objectionable. Some believe that a preservative is necessary only when the syrup is not properly and carefully prepared. Harries[10] expressed the opinion that if hypophosphorous acid prevented the decomposition of the syrup in the bottle it might do the same in the stomach, and in such a way alter the therapeutic value and efficiency. Alpers[11] carried out a series of experiments and concluded that a preservative is not essential. He states, "Syrup of Iodide of Iron made from the best ingredients does not need any preservative to remain perfect on the shelves of the shop. The samples with hypophosphorous acid kept equally as well as those without it, but its addition is neither an advantage or a necessity. After dispensing, or when bottles

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[1] Cook, JOUR. A. PH. A., 6, 75 (1917).

[2] Wilkening, *Süddeut. Apoth.-Ztg.*, 373 (1917), through *Pharm. Zentrahl.*, 59, 301, through "Digest of Com." (1918).

[3] Beringer, *Am. J. Pharm.*, 86, 358 (1914).

[4] *Süddeut. Apoth.-Ztg.*, 64, 182 (1925); through A. PH. A. YEAR BOOK, 12, 76 (1925).

[5] Anon, *Am. Drug.*, 11, 13 (1923); through "British Year Book," 404 (1924).

[6] Meier, *Drug. Circ.*, through *Am. J. Pharm.*, 49, 134 (1877).

[7] England, *Am. J. Pharm.*, 60, 547 (1888).

[8] Izard, *L'Union Pharm.*, 102 (May 1883); through *Am. J. Pharm.*, 55, 402 (1883).

[9] Noblet, A. PH. A. YEAR BOOK, 2, 76 (1913).

[10] Harries, *Pharm. J.*, London, 28, 366 (1909); through "Digest of Com." (1909).

[11] Alpers, JOUR. A. PH. A., 3, 420–423 (1914).

are opened several times a day, citric acid is the best preservative; but its power seems to be restricted to a limited time, after which discoloration takes place rapidly." Beringer[1] objected as did Cook,[2] because it caused the color of the finished syrup to be darker. Thum[3] believed that the use of preservatives in either food or drugs should not be encouraged.

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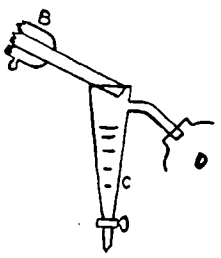
(To be continued)

COMBINED OPERATION FOR DETERMINATION OF WATER AND PHENOLS IN COMPOUND SOLUTION CRESOL, U. S. P.

BY HUBERT H. OHAYER.

The directions for assaying Compound Solution Cresol given in the U. S. P. specify that 50 cc. of the solution, 150 cc. of kerosene, purified by shaking out with NaOH solution, and 3 Gm. $NaHCO_3$ be placed in a 500-cc. distilling flask and distilled to decomposition of the residue. In a laboratory where it is necessary to have a check on both the phenol and water content of the finished solution, the water assay can be quickly and easily combined with that of the phenols in the following simple manner.



The water and the kerosene-phenol solution are distilled from the flask at A through the condenser B and into the little trap C where the water remains and the lighter than water mixture flows over through the outlet tube into the separatory funnel D directed by the U. S. P. as the receiver for the phenol assay distillate. The trap is graduated in tenths of a cc. and has a capacity of 10 cc. It can be purchased easily and may or may not be fitted with a stop-cock at the bottom. The amount of water is read off, multiplied by two gives the percentage of water originally present in the Compound Solution. The contents of the trap may then be rinsed into the separatory funnel and the phenol assay proceeded with as directed in the U. S. P.

The author has purified kerosene by shaking it out with NaOH solution as directed and has then distilled it through this apparatus and found that not enough water is dissolved by the kerosene to affect the accuracy of the method.

PARKE, DAVIS & CO.,
DETROIT, MICH.

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[1] Beringer, *Am. J. Pharm.*, 86, 358 (1914).

[2] Cook, PROC. A. PH. A., 56, 958 (1908).

[3] Thum, BULL. A. PH. A., 5, 646 (1910); *Am. Drug.*, 57, 130; PROC. A. PH. A., 58, 1265 (1910).