

## SYRUP OF TOLU.

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The freshly prepared syrup of tolu made by the U. S. P. X process has a yellow color. On standing the syrup darkens, not infrequently becoming dark brown if the syrup is kept for a period of months. Curiously the syrups of tolu dispensed by some pharmacists are colorless and insipid liquids. These syrups are usually slightly acid and are decidedly inferior in odor and taste to those made by the official process.

Although a colorless, weakly acid syrup of tolu may be prepared comparable in odor, taste and therapeutic value to one made by the prescribed formula, it is an advantage in pharmaceutical practice to have either a neutral or slightly alkaline syrup. However, neutral and alkaline syrups of tolu are always colored, the intensity of the color increasing with an increase of the hydroxyl-ion concentration of the syrups.

Syrup of tolu contains the alcohol-water soluble constituents of balsam of tolu in the proportion of 1 Gm. of the latter to 100 cc. of the finished syrup. For the sake of convenience the official tincture of tolu is used. The syrup, therefore, contains about 4% of alcohol by volume.

The principal therapeutic agent of the official syrup is cinnamic acid in the form of its magnesium salt. The U. S. P. X does not prescribe a standard for the free cinnamic acid content of balsam of tolu. Hence, it is to be expected that great variations will be found in the cinnamic acid content of syrups of tolu obtainable

TABLE I.

	I.	II.	Color.	Litmus.	Phenol-phthal.	Conc. HCl.	Sol. NaOH.	Color on Standing.	Methyl Violet.
1	10.0	..	y	Blue	Red	Ppt. cd	Darker	.....	Bluish
2	2.0	50	y	Blue	Pink	Ppt. cd	Darker	Orange 32	Bluish
3	1.5	50	ly	Blue	nc	Ppt. cd	Darker	Orange 32	Bluish
4	1.0	50	py	Blue	nc	Ppt. cd	Darker	Yellow 32	Bluish
5	0.6	50	nc	Red	nc	Ppt. ..	Yellow	.....	Bluish
6	...	50	nc	Red	nc	.....	py	.....	Bluish
7	Fluid	Tolu	nc	Red	nc	.....	....	.....	Violet

I Mag. Carb. II Talcum, y, ly, py, yellow, light yellow, pale yellow, respectively; nc no color, cd color discharged, ppt. precipitate, 32 number of days in contact.

TABLE II.—SOLUBILITY OF CINNAMIC ACID IN ALCOHOL-WATER SOLUTIONS AT 18°-19° C.

Alcohol, % by volume..	0	1.06	3.9	5.0	10.0	15.0	20.0	24.7	27.2	30.1
Cinnamic acid, Gm. per										
L. sol.....	0.417	0.43	0.5	0.53	0.58	0.73	0.92	1.18	1.5	1.84
Total HCl in Gm. per L.										
sol.....	.....	.....	.....	.....	9.71	9.86	10.05	10.31	10.63	10.97

in the open market. Tschirch (1), Vezes et Dupont (2) and Dieterich (3) all state that balsam of tolu contains from 12 to 15% of free cinnamic acid. The latter calls attention to a steady decrease in the free cinnamic acid content of balsams of tolu delivered in the Hamburg market. Hager (4) as well as Tschirch (1) refer to the work of Spillsbury and Joyce who state that good balsam of tolu contains at least 18% of free cinnamic acid. The latter figure is also given by the National Dispensatory.

The magnesium carbonate of the official process serves a twofold purpose. It acts as an adsorbent for the water-insoluble portion and reacts with the free acids of the balsam to form the more soluble magnesium salt. Calcium phosphate, talcum (5) and fine sand are also used as adsorbents. The syrups made by using the latter three are merely flavored sugary solutions of the free acids. Nothing seems to have been published about the coloring substance of syrup of tolu. This substance is colorless in acid solutions and yellow in alkaline solutions.

Many manufacturers of pharmaceuticals market a preparation called "Fluid Tolu Soluble." This product when mixed with simple syrup is supposed to give the official syrup. Lately, some manufacturers have omitted the word official. The fluids tolu soluble are, therefore, concentrated solutions of the hydro-alcoholic soluble components of the balsam. These concentrated solutions are mostly colorless and yield syrups whose color does not change on standing. They are, however, deficient in both odor and taste. Examination of the catalogs of various manufacturers reveals a lack of uniformity in the alcohol content and in the proportion of mixing of the fluid tolu with the simple syrup. All of these concentrations give syrups of a lower alcohol content than the official syrup. Still greater differences are noticeable when a fluid of tolu is compared with the filtrate obtained by the official procedure. The comparison was extended to include solutions made with smaller quantities of magnesium carbonate together with talcum and talcum alone. All of these were prepared without sugar. In some of these tests the mixtures were kept unfiltered for one hour to four weeks. The fluid of tolu tested was labeled to contain 27% of alcohol by volume. The results are listed in Table I.

These tests show that the concentration and intensity of the dissolved coloring substance is a function of the hydroxyl-ion concentration. The coloring substance is slightly soluble in weakly acid solutions in its colorless form. These solutions become colored upon the addition of an alkaline solution.

The coloring substance is abstracted from both the acid and alkaline solutions by wool. When this wool is dyed with methyl violet it takes on a bluer shade than wool dyed with methyl violet only. A few drops of a solution of methyl violet added to the solutions enumerated in Table I impart to them a color which is blue by transmitted light and turbid coppery by reflected light. The turbidity is greatest in alkaline solutions from which the coloring matter soon precipitates. In weakly acid solutions the blue color is noticeable only by comparing it with the color of an equal quantity of methyl violet in distilled water. When to one drop of tincture of tolu, diluted with alcohol, water is added until the solution becomes but slightly turbid, the addition of methyl violet solution and one drop of solution of sodium hydroxide produces a red color which turns blue upon the addition of a large quantity of water. This change in the color of the methyl violet is probably due to the adsorption of the yellow coloring substance of the solutions tested by the methyl violet.

Many other substances have a similar effect upon methyl violet. Dilute solutions of *p*-nitrophenol, picric acid, 3,4-nitrochlorbenzenesulphonic acid, salicylic acid and anilin appear bluish to a greater or lesser degree upon the addition of methyl violet. Neither solutions of cinnamic, gallic and tannic acid nor nitrobenzene give such a color change. A saturated solution of picric acid to which methyl violet has been added forms a precipitate which upon dispersing by shaking appears

green by transmitted light. Upon diluting this mixture with a large quantity of water the transmitted light becomes blue.

The fluid tolu soluble compared with the solutions listed in Table I shows a somewhat similar behavior as Solution 6 in which only talcum was used as the adsorbent. The latter solution may be considered as a saturated solution of cinnamic acid containing in addition small quantities of odor and taste-bearing substances, a coloring substance in its colorless form and approximately 8.3% of alcohol by volume. However, the fluid tolu contained 27% of alcohol and was labeled to give the official syrup in the proportion of 1 to 20 parts of the finished syrup. Therefore, it should be over nine times stronger than the solution obtained by the official process. Consequently, by the addition of conc. HCl a voluminous precipitate of cinnamic acid should be formed. The absence of a precipitate and the lack of color changes by the addition of methyl violet and alkali solutions casts a doubt upon the origin of this fluid tolu.

The solubility of a substance in water is usually considerably changed by the addition of other soluble substances. This change in solubility may be calculated when the physical constants involved are known. The change in solubility of a substance by the addition of a small quantity of another is frequently very small and for practical purposes may be neglected. Thus, it will be assumed that the maximum amount of cinnamic acid and magnesium cinnamate contained in the fluid tolu is identical with their solubility in an alcohol-water mixture of similar alcoholic content. Since no solubility data of either cinnamic acid or magnesium cinnamate in alcohol-water mixtures have been published, these were determined at a temperature between 18° and 19° C. As no thermostat was available the solutions were kept in a closet which was known to have a fairly constant temperature. After two weeks during which the solutions were shaken frequently, the solutions containing some of the solid phase were transferred to a room the temperature of which was practically constant. The temperatures of the room and of the solutions were observed frequently and after two hours the solutions were filtered into dry flasks. The concentrations of the filtered solutions were determined as time presented itself. The solubility of each in commercial distilled water was also determined.

The solubility of HCin in water at varying temperatures was determined by Mayer (6) who found the values at 18° and 25° C. to be 0.420 and 0.546 Gm., at 25° C. by Loevenharz (7) as 0.491 Gm. and by Larsson (8) as 0.495 Gm., all per l. of solution. The dissociation constant at 25° C. was determined by Ostwald (9) as  $3.55 \cdot 10^{-5}$  and by Larsson (10) as  $3.8 \cdot 10^{-5}$ . Since the dielectric constant of alcohol is less than that of water it follows that the ionization of substances in alcohol-water mixtures decreases with the increase in the alcohol concentration of the solution. This effect is largely eliminated by diluting the solution with a large volume of water.

The required indicator for the titration of HCin may be calculated by considering the base, salts and the colored form of the indicator completely ionized. At the end-point the rates of reaction between the base and the indicator and the salt of the indicator and the acid should be equal. Therefore  $k_i/k_w = k_a/k_i$  or  $k_i^2 = k_a k_w$ , where  $k_i^2$  is the indicator constant and  $k_a$  and  $k_w$  are the dissociation constants of the acid and water, respectively. Substituting the proper values

in the above equation and writing it in the form  $\text{pk}_i = \frac{1}{2}(\text{pk}_a + \text{pk}_w) = 18.45/2 = 9.23$  the required indicator constant is determined. Phenolphthalein may therefore be used as the indicator in the titration of HCin. The solutions were titrated with a 0.1125*N* solution of sodium hydroxide. The alcohol effect was practically eliminated by diluting the solutions so that the alcohol content was less than 2.5% by volume. The results are represented in Table II and graphically by the solubility Curve A.

Magnesium cinnamate is the salt of a weak acid and base, and since HCin is quite volatile, it cannot be prepared by the evaporation of its aqueous solution by means of heat. It may, however, be made easily by the interaction of a solution of an alkali cinnamate with a concentrated solution of a magnesium salt, provided that the resulting salts are more soluble than the magnesium cinnamate. Nearly complete separation may be attained if the mol concentration of the alkali cinnamate is small compared to that of the magnesium salt.

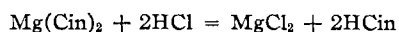
Beilstein (11) lists three salts each with 1, 2 or 3 molecules of water of crystallization. Tarugi and Checchi (12) refer to a salt containing 3 molecules of water, but do not give its method of preparation. Ephraim and Pfister (13) prepared a salt containing 4 molecules of water by adding  $\text{MgSO}_4$  to a solution of NaCin. The solubility of this salt in water was determined by them at 20° C. as 12.25 Gm. per L. of solution.

For the determination of the alcohol-water solubility of magnesium cinnamate a sufficient quantity of it was prepared by adding a solution NaCin equivalent to 8 Gm. HCin to a saturated solution containing 240 Gm. of  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ , stirring the solution rapidly. Crystals of magnesium cinnamate appeared immediately. After standing for some time the crystals were transferred to a filter, washed several times with ice cold water and finally with alcohol. The crystals were dried between filter paper at room temperature and transferred after three days to a glass-stoppered bottle.

This magnesium cinnamate crystallized in the form of small white, odorless and tasteless leaflets. Upon analyzing 0.113 Gm. of this salt for magnesium by the pyrophosphate (14) method it yielded 0.0321 Gm. of  $\text{Mg}_2\text{P}_2\text{O}_7$ . This corresponds to 0.1126 Gm. of magnesium cinnamate of the formula  $\text{Mg}(\text{Cin})_2 \cdot 4\text{H}_2\text{O}$ . It is, therefore, identical to the salt prepared by Ephraim & Pfister (13).

The solutions of this salt in water and alcohol-water yielded upon analysis nearly identical quantities of  $\text{Mg}_2\text{P}_2\text{O}_7$ . The average of all of the 5-cc. solutions was 0.0172 Gm. of  $\text{Mg}_2\text{P}_2\text{O}_7$ . This is equivalent to 12.07 Gm. of  $\text{Mg}(\text{Cin})_2 \cdot 4\text{H}_2\text{O}$  per L. of solution. The solubility of this salt in alcohol-water solutions up to 30% of alcohol by volume is the same as that in water. Magnesium benzoate is also similarly soluble in both solvents.

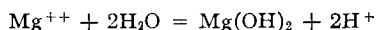
The above result was checked by titrating the solutions of  $\text{Mg}(\text{Cin})_2$  with a standard solution of HCl. In the reaction



at completion both  $\text{MgCl}_2$  and HCin are present in the solution. When 5 cc. of a saturated solution of  $\text{MgCin}_2$  at 20° C. is diluted to a volume of 50 cc. the concentration of the solution becomes  $6.28 \cdot 10^{-3}$  Gm. equivalents. Since the solubility of HCin at the same temperature is  $2.82 \cdot 10^{-3}$  Gm. equivalents, upon the addition

of HCl solid cinnamic acid separates from the solution. The  $H^+$  concentration of a saturated aqueous solution of HCin may be computed by means of the relation  $H^+ = (k_{a,c_a})^{1/2}$  and is  $3.16 \cdot 10^{-4}$  Gm. equivalents per L. of solution.

The magnesium chloride formed in the reaction decreases the solubility of the cinnamic acid. The consequent reduction of the  $H^+$  concentration of the solution is offset by the hydrolyses of the  $Mg^{++}$  according to the equation



The degree of hydrolyses of  $MgCl_2$  at a dilution of 16 L. per mol. was determined at  $100^\circ C.$  by Kullgren (15) as  $2.66 \cdot 10^{-3} \%$  per mol. Data for lower temperatures do not seem to have been published. As an approximation it may be assumed that the salting out effect of the  $MgCl_2$  is nearly compensated by its hydrolyses so that the  $H^+$  concentration of the solution at the end-point of the titration is about that of a saturated solution of HCin. The indicator constant of methyl orange

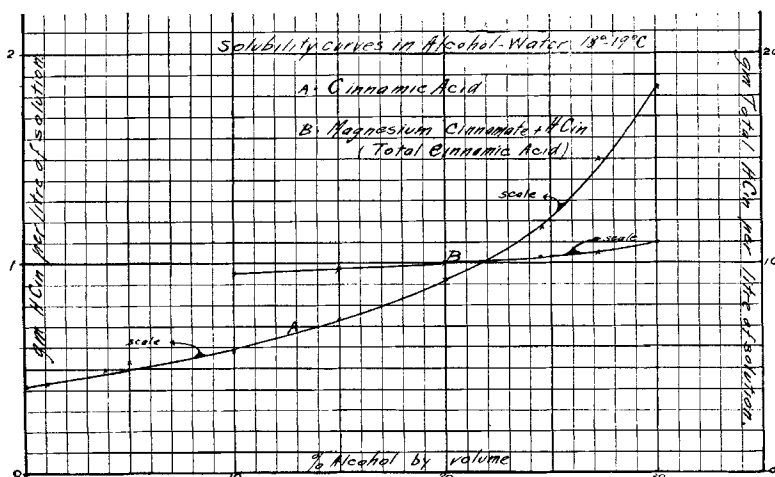


Fig. 1.

is  $5 \cdot 10^{-4}$ , consequently the  $H^+$  concentration of  $3.16 \cdot 10^{-4}$  is equivalent to 60% of a conversion of the color of methyl orange from yellow to red. To facilitate the detection of the end-point a color standard was prepared by dissolving a small quantity of cinnamic acid in alcohol adding the required amount of indicator and diluting to 50 cc. with water. The separated HCin adsorbs a large portion of the methyl orange necessitating the addition of a larger quantity of this indicator.

In the titrations 5- and 10-cc. portions of the solutions were diluted to 50 cc. and titrated with a  $0.1185N$  HCl solution. Each 5 cc. required 2.6 cc. of the acid which is equivalent to 12.03 Gm. of  $MgCin_2 \cdot 4H_2O$  per L. of solution. This corresponds to 9.13 Gm. of HCin. The previously found value by the pyrophosphate method is 12.07 Gm.  $MgCin_2 \cdot 4H_2O$ .

The solubility of  $MgCin_2$  and HCin in the presence of each other in solutions containing 10% and more of alcohol by volume is practically identical to their individual solubility. The total HCin content of such solutions may consequently be obtained by adding 9.13 Gm. to the solubility values obtained for HCin alone. This is shown in Table II and is also represented by Curve B.

From the foregoing it is now possible to calculate the maximum quantity of total HCIn that may be present in the fluid tolu soluble of an alcohol content of 27% by volume. In the proportion of 1 part of the fluid to 20 parts of finished syrup, 50 cc. are required to make 1 L. of syrup. The total quantity of HCIn that will dissolve in a L. of solution containing 27% of alcohol is 10.6 Gm. Therefore, the maximum amount of total HCIn in 50 cc. of the fluid of tolu is 0.53 Gm. This is equivalent to a balsam of tolu containing 5.3% of free HCIn. The fluid of tolu that was examined, however, did not contain  $\frac{1}{20}$  of the theoretical amount. Some of the fluids tolu listed in the catalogs of the manufacturers are directed to be mixed in the proportion of 1 to 12 give syrups that may contain more total HCIn than the former, but, not to exceed 0.83 Gm. per L. of syrup. This, then, definitely establishes the fact that at their best the fluids tolu soluble designated to be used to make the official syrup are equivalent only to those made of the poorer grades of balsams of tolu. The one fluid of tolu investigated was nearly devoid of HCIn and was practically only a flavored hydro-alcoholic solution.

The addition of water to a triturated mixture of tincture of tolu and magnesium carbonate precipitates the resins, esters and most of the acid. The resins and esters are adsorbed by the magnesium carbonate and the precipitated acid forming more or less perfect diffusion cells. The number of particles within the cells depends upon the number of all particles present and the degree of trituration. The distribution of the particles between the various cells will not be uniform, and if the ratio of the magnesium carbonate to the acid is large many cells will contain only particles of magnesium carbonate. Since each cell represents an individual reaction chamber much coloring substance will be dissolved before the reaction between the acid and carbonate is completed. If an inert adsorbent is substituted for part of the carbonate the time for the completion of the reaction between the carbonate and the acid is increased.

A more satisfactory procedure to practically eliminate the coloring substance is to substitute a solution of a neutral or nearly neutral reactant and an inert adsorbent for the magnesium carbonate. The most commonly accessible substances of this type are sodium bicarbonate and talcum. Sodium bicarbonate reacts with the HCIn of the balsam of tolu to form sodium cinnamate. This was introduced to the medical profession under the name of "Hetol" and was used at one time in the treatment of tubercular infections. It is freely soluble in water and in alcohol-water solutions.

In their aqueous solutions both  $\text{NaHCO}_3$  and HCIn are hydrolyzed and since the dissociation constant of carbonic acid  $\text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$  is nearly  $\frac{1}{100}$  that of cinnamic acid, it follows that at the completion of the reaction between  $\text{NaHCO}_3$  and HCIn the hydroxyl-ion concentration of the solution decreases to nearly  $\frac{1}{10}$  of its original value. When both the acid and salt are in solution the reaction is rapidly completed. This can be accomplished by adding only sufficient water to the tincture of tolu to precipitate the resin and esters. These are adsorbed by the talcum forming nearly neutral cells instead of the distinctly alkaline ones when magnesium carbonate is used. The reaction between the bicarbonate and the coloring substance is consequently reduced to a minimum, particularly if all the operations are rapidly completed. A slight excess over the theoretical amount of sodium bicarbonate is required to bring all of the cinnamic acid into solution.

This was found to be 5% giving a factor 0.6 so that the required sodium bicarbonate may be calculated by means of the formula  $x = 0.6a/10$ , where  $a$  is the percentage of cinnamic acid of the balsam of tolu.

The suggested formula and procedure for syrup of tolu are

Tincture of tolu	50 cc.
Talcum	50 Gm.
Sodium bicarbonate	
Sugar	
Distilled water	q. s. 1000 cc.

First prepare a well-wetted folded filter, next dissolve the sodium bicarbonate in 50 cc. of distilled water calculated by the formula  $x = 0.6a$ , where  $a = \%$  of HCin in the tincture of tolu. Triturate the talcum and tincture intimately, add 25 cc. of water triturating until a smooth mixture is formed, now add at once the solution sodium bicarbonate followed while triturating by 250 cc. of water, transfer to the filter. Wash the mortar with water and transfer to filter. When all has run through the filter add sufficient water to the filter to obtain 480 cc. of filtrate. To this add the sugar and dissolve.

The filtrate has a faintly yellowish color yielding a nearly colorless syrup. It is slightly alkaline to litmus, gives a copious precipitate with HCl, a slight yellow color with alkali solution and a bluish color with methyl violet solution. The resulting syrup has a highly aromatic odor and taste and remains nearly colorless on keeping.

#### SUMMARY.

Balsam of tolu contains a substance which is yellow in alkaline solutions and colorless in acid solutions. This coloring substance gives a bluish color to methyl violet solutions. It causes the darkening of the official syrup.

The fluids tolu soluble at their best are representative of the poorer grades of balsam of tolu. The one investigated proved to be a flavored alcohol-water solution.

The solubility of cinnamic acid and magnesium cinnamate in alcohol-water mixtures was determined with an accuracy sufficient for the purpose of this investigation.

A formula for syrup of tolu using sodium bicarbonate is given. It is finally suggested that a standard for the cinnamic acid content of balsam of tolu be adopted in the next revision of the Pharmacopœia.

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