THE COMPOUNDING OF TEN TROUBLESOME PRESCRIPTIONS

by

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The subject of this thesis was taken from a paper read by Mr. Kaemmerer* before the American Pharmaceutical Association in September, 1905, in which he briefly discussed the methods of compounding about thirty prescriptions. It includes work on ten of the most important prescriptions mentioned by Mr. Kaemmerer, especially those in which the difficulty in compounding is due to some chemical or pharmaceutical incompatability. Each prescription was worked upon in the laboratory and the literature at hand thoroughly consulted with a view of remedying the difficulty from the standpoint of the compounder.

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*Proc. A. Ph. A., 53, p. 421.

Prescription No. 1.

The first of the prescriptions considered reads as follows:

Pyrophosphate of Iron	2 dr.
Dilute Phosphoric acid	6 fl. dr.
Syrup, a sufficient quantity to make	3 fl. oz.

Directions: A teaspoonful in water an hour before meals.

This prescription, or a similar one containing pyrophosphate of iron in combination with phosphoric acid, has caused a great deal of annoyance to pharmacists for the last fifty years or more. It is not positively known just when it was first presented to the American pharmacist, but the first mention of it in American literature is to be found in the Druggists Circular of 1859.* It is probably of foreign origin, as Persoz, of Strassburg, Germany,** first indicated the employment of a soluble pyrophosphate of iron, while a few years later M. Robiquet, a Frenchman, used it extensively in the preparation of a syrup*** in which however no phosphoric acid

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* Am. Drug. Cir., 3, p. 127.
** Year Book Pharm., 1876, p. 352.
*** Am. Jour. Pharm., 31, p. 248.

was employed. The reason for introducing phosphoric acid is to be found in the fact that the contents of the stomach are acid and that it was desired to have the iron salt in the best possible condition for absorption. The presence of the acid, was for the purpose of making the preparation approach as nearly as possible, the condition of the liquids in the system. For the same reason lactic and hydrochloric acids are used in such preparations as Syrup of Calcium Lactophosphate and Syrup of the Chlor-hydrophosphates of iron.* As is well known, acids tend to cause a precipitation of the iron salt, and, as the pyrophosphate is now narly always prescribed in combination with phosphoric acid, it will readily be seen why so many pharmacists have been troubled with the compounding of this prescription.

The remedies suggested for holding the iron salt in solution have been numerous. The addition of the following substances has been proposed at one time or another: pyrophosphate of soda,** ammonia water,*** ammonium citrate,**** potassium carbonate***** and syrup of citric acid, and sodium phosphate.****** Dr. G. M. Baker,

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* Year Book, Pharm., 1876, p. 352.
** Am. Drug. Circ., 26, p. 76.
*** Am. Drug. Circ., 22, p. 198.
**** Am. Drug. Circ., 24, p. 92.
***** Am. Drug. Circ., 25, p. 74.
****** Am. Drug. Circ., 45, p. 150.

at a meeting of the Kings County Pharmaceutical Society in 1880,* says in reference to this incompatability: "A pure tribasic acid will afford neither precipitation nor cloudiness." In direct contradiction to this, the substitution of the meta-phosphoric for the ortho-phosphoric acid has been recommended by many authors.**

These different methods of preventing precipitation will be taken up, one at a time, and fully discussed. The propriety of making additions or substitutions in prescriptions without consulting the physician is a somewhat open question and will not be considered here. Since the difficulty in compounding the aforesaid prescription is the precipitation of the iron salt, the first step toward solving the problem will be to ascertain the composition of pyrophosphate of iron.

There are a number of methods for the preparation of this salt, only two of which need be mentioned as the others are merely modifications of these. The main differences in these two methods is that in one ammonium citrate,*** and in the other sodium citrate,****

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* Am. Drug. Circ., 24, p. 92.
** Am. Drug. Circ., 22, p. 198.
Am. Drug. Circ., 26, p. 92.
Am. Drug. Circ., 36, p. 158.
Am. Drug. Circ., 33, p. 254.
Am. Drug. Circ., 31, p. 38.
Am. Drug. Circ., 28, p. 122.
*** Am. Jour. Pharm., 31, p. 248.
**** Am. Drug. Circ., 34, p. 27.

is employed to render the iron salt soluble. Pure pyrophosphate of iron is a white powder, insoluble in water, acids, and all ordinary solvents. It is soluble, however, in the alkaline citrates and it is for this reason that they are used in the preparation of the soluble salt. The soluble pyrophosphate of iron was first prepared with ammonia water and citric acid, this being the means of obtaining ammonium citrate. The first published analysis of this preparation is that of a Frenchman, M. Robiquet, in 1859*, who reports the following results:

Pyrophosphate of iron (anhydrous)	64.736 %
Citrate of ammonium	28.967 %
Water of combination	6.315 %

Since then, many references have been made to the solubility of pyrophosphate of iron in the alkaline citrates, some pharmacists using potassium or sodium citrate in preference to the ammonium salt.** In the U. S. Pharmacopea of 1880, the process for making this salt was modified by replacing the ammonium citrate, previously used, with sodium citrate the result being a more stable compound. Owing to the loss of ammonia, the pyrophosphate prepared with its aid, upon standing, became partially insoluble. This difficulty could be

* Am. Jour. Pharm., 31, p. 248.
** Proc. Am. Ph. Assoc., 28, p. 460.

overcome by adding a few drops of ammonia water and driving off the excess by heating,* but when sodium citrate was used the resulting compound was stable and consequently this salt was adopted. A solution of the compound prepared with sodium citrate is also much better in appearance, having a bright green color, while that prepared with the ammonium salt is of a reddish brown color. The method of preparing soluble pyrophosphate of iron consists in adding a solution of sodium pyrophosphate to a solution of ferric citrate and evaporating the liquid to a syrupy consistency when it is spread out on smooth plates to scale. The ferric pyrophosphate produced, dissolves in the sodium citrate, also produced, with the formation of a double salt of ferric pyrophosphate and sodium citrate. In the preparation of soluble pyrophosphate of iron a considerable excess of sodium pyrophosphate is used. The excess of sodium pyrophosphate also aids in dissolving the ferric phrophosphate forming a double pyrophosphate of iron and sodium.

As has been mentioned, soluble pyrophosphate of iron has been prepared with the aid of sodium and ammonium citrates, a certain definite proportion being necessary to hold the iron salt in solution. Now, it is evident that if any acid other than citric acid be

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* Am. Drug. Circ., 22, p. 198.

added to this double salt, citric acid will be liberated and the other acid will at least partially take its place. As this decreases the amount of alkaline citrate present a precipitation of ferric pyrophosphate occurs. The same thing happens with the double pyrophosphate of iron and sodium if acid is added to it.

It has been mentioned by Campbell*, Perkins,** and others that a certain proportion of acid, with reference to the amount of pyrophosphate of iron used, may be added without the formation of a precipitate. The following tabulation by campbell shows the results obtained by the use of different amounts of ortho phosphoric acid, the solutions being made up with water to 2 fl. oz.

	Ferric pyrophosphate.	Dilute phosphoric acid.	Result.
No. 1	1 dr.	1 fl. dr.	clear solution
No. 2	1 dr.	2 fl. drs.	clear solution
No. 3	1 dr.	3 fl. drs.	cloudy solution
No. 4	1 dr.	4 fl. drs.	precipitate
No. 5	1 dr.	1 fl. oz.	precipitate

We see here that the amount of dilute phosphoric acid which may be used with 1 drachm of pyrophosphate of iron without causing a precipitate is between 2 and 3 fl. drachms, as with two fl. drachms a clear solution

* Am. Drug. Circ., 34, p. 27.
** Am. Drug. Circ., 26, p. 76.

results and with 3 fl. drachms a cloudy solution results. Perkins says that 6 fl. drachms of official dilute phosphosic acid to 2 drachms of pyrophosphate of soda is the maximum amount which may be used without causing precipitation. If this proportion is not exceeded an elegant green solution results. Upon adding acid in slight excess over this proportion a cloudy mixture is obtained and if considerable excess of acid is added, a heavy gelatinous precipitate is formed.

The prescription in question contains phosphoric acid and pyrophosphate of iron in the proportion of 6 fl. drachms of acid to 2 drachms of pyrophosphate of iron and yields a slightly cloudy mixture. By referring to Mr. Campbell's tabulation we see that this corresponds with his experiments and we also see that if the amount of phosphoric acid be slightly diminished a clear solution will result. As a matter of fact, when the prescription is prepared with 5 1/2 fl. drachms of dilute phosphoric acid in place of 6 fl. drachms, a clear solution is obtained.

With the exception of the addition of ammonia water and the substitution of meta phosphoric acid for ortho phosphoric acid, the methods used for preventing precipitation in prescriptions of this kind are all practically the same, viz; the addition of alkaline

citrate. This is the most feasible and rational remedy, for by this means the percentage of citrate in the solution is raised without interfering with the total acidity of the solution. Enough alkaline citrate must be added to bring the ratio of citrate to phosphoric acid above the limit above shown. The excess of phosphoric acid immediately reacts with the alkaline citrate added thereby decreasing the amount of free phosphoric acid in the solution. As soon as it is reduced so that not more than 5 1/2 fl. drachms of the dilute acid are present for every drachm of pyrophosphate of iron a clear solution results. Undoubtedly potassium and sodium citrates are the best means of making this addition as they are fairly stable and are found in most drug stores. Since the ammonium salt of citric acid is rather unstable and especially when it has been kept for some time may have been almost completely changed to citric acid it is a very uncertain means of adding alkaline citrate. Ammonium citrate has been added in the form of ammonium carbonate and citric acid. The only objection to this method is that it is a rather roundabout way of accomplishing a simple operation.

The addition of alkaline citrate in no way interferes with the action of phosphoric acid though it necessarily lowers the percentage of free phosphoric

acid in the solution and, in prescriptions where this addition has been made, the total acidity will always be the same in relation to the amount of pyrophosphate of iron used.

The use of sodium phosphate to prevent precipitation is essentially the same as adding more citrate for when this is added some must be reacted upon by the citric acid in the solution, thus increasing the amount of alkaline citrate present. More alkaline phosphate is required than citrate however as some phosphoric acid is also introduced. The use of sodium pyrophosphate gives practically the same result as sodium phosphate. Sodium pyrophosphate also has the power to dissolve some pyrophosphate of iron in neutral solution.

The use of ammonia water or caustic alkali is the easiest means of decreasing the percentage of free phosphoric acid but it also decreases the total acidity and, as it is in comparatively strong solutions, enough might be added to neutralize all of the free acid before the operator becomes aware that enough has been added to produce the clear solution desired. As has been mentioned, the acidity of the mixture is intended to insure immediate assimilation of the pyrophosphate of iron in the stomach, and for this reason anything which will

decrease the acidity of the mixture should not be added.

The substitution of meta phosphoric acid for ortho phosphoric acid is a remedy, used to prevent precipitation of pyrophosphate of iron in this prescription, which has been used more than any other. The reason that no precipitation occurs when this substitution is made is that there is a considerable difference in the acidity of these two acids. Meta phosphoric acid has been introduced into the National Formulary simply because it is used in prescriptions of this kind. Nevertheless, on account of the difference in acidity of meta and ortho phosphoric acids, it should not be used unless a correspondingly larger amount be added. As is seen by the following reactions it requires 236.52 gms. of meta phosphoric acid to react with the same amount of alkali with which 97.8 gms. of ortho phosphoric acid will react.

$$Na_3C_6H_5O_7 + H_3PO_4 = H_3C_6H_5O_7 + Na_3PO_4$$

97.8

$$Na_3C_6H_5O_7 + 3HPO_3 = H_3C_6H_5O_7 + 3NaPO_3$$

3 X 78.84

Hence about 2 1/2 times as much metaphosphoric acid is required to produce the same acidity which orthophosphoric acid will produce. If this amount of metaphosphoric acid is used, precipitation will occur the same as with ortho phosphoric acid. Meta phosphoric acid in the

presence of water quite readily takes up a molecule of water becoming ortho phosphoric acid. This change gradually takes place and a corresponding increase in the acidity of the solution will occur. Hence in a prescription where an equal amount of meta phosphoric acid has been substituted for ortho phosphoric acid the acidity increases upon standing and in a short time the solution becomes nearly as acid as if the ortho phosphoric acid were used. Then when the amount of acid gets above the maximum amount with which a clear solution may be obtained, precipitation occurs. Conditions modify the conversion of meta phosphoric acid into ortho phosphoric acid, heat and light being the necessary agents which bring about the change. A prescription is very liable to be subjected to these conditions and the change would most likely be complete before all of the medicine was used.

The trouble in this prescription is therefore caused by an excess of phosphoric acid. The best means of remedying this fault is to reduce tha amount of free phosphoric acid without reducing the total acidity of the mixture, and this is preferably done by adding a small amount of sodium or potassium citrate, the amount depending upon the amount of free acid in the solution.

Prescription No. 2.

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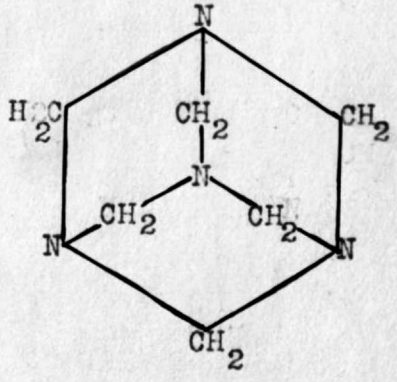
Calomel	1 grain
Urotropin	1 drachm

Mix. Divide into 12 powders.

Directions: one every four hours.

If prepared in a perfectly dry atmosphere these substances can be mixed without any decomposition whatever. If mositure is present when these substances are rubbed together a black mixture will result. Under ordinary conditions a mixture of these substances will gradually turn black and they are therefore called incompatabile as some new compound certainly must be formed.

Urotropin is the trade name for a complex compound, Hexamethylene titranine, having the following formula:



It is prepared by the action of ammonia on formaldehyde. It is monobasic, one of its nitrogen atoms

still having additive capacity. Two this can be added two atoms of hydrogen, the elements of a molecule of water, hydrocyanic acid, and other acids.

The chemical properties of urotropin can be likened to ammonia which is also a monobasic nitrogen compound. The action of ammonia on calomel in the presence of water is well known. A black compound, whose composition has not been determined with certainty, is produced. Some chemists regard it as mercurous ammonium chloride, $(NH_2Hg_2)Cl$. The reaction explaining the formation of this compound is as follows:

$$Hg_2Cl_2 + 2NH_3 Aq. = (NH2Hg2)Cl + NH_4Cl\ Aq.$$

If analogous, the reaction of urotropin with calomel would be as follows:

$$Hg_2Cl_2 + 2C_6H_{12}N_4\ Aq. = (C_6H_{11}N_4Hg_2)Cl + C_6H_{13}N_4Cl\ Aq.$$

Some of the black compound was obtained by treating calomel with urotropin in presence of water. Some of the supernatant liquid was filtered and tested, for soluble mercury salts, with hydrogen sulphide. The liquid merely turned a dark color, no precipitate being formed. The filtrate obtained from the same amounts of calomel and water was tested in a similar manner, the results being the same, proving that by the action of urotropin on calomel no soluble mercury compound is

formed. Next the precipitate was well washed by decantation, to be sure no organic matter would be introduced, and dried and ignited on a porcelain crucible cover. White vapors of calomel were given off, the residue becoming charred and, upon further heating, igniting, thus showing the presence of carbon. Another portion of the precipitate was heated in a crucible with lime. The odor of ammonia was evolved and upon holding a glass rod, previously dipped into hydrochloric acid, over the crucible, white vapors of ammonium chloride were formed. This proved the presence of nitrogen in the compound.

As both nitrogen and carbon were found in the compound it is quite safe to assume the presence of the urotropin molecule and, as all free urotropin in the mixture would be removed by washing, it must be in combination with the calomel. The incompatability is therefore due to the formation of a compound similar to that formed by calomel and ammonia.

Prescription No. 3.

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Potassium bicarbonate	3 drachms
Potassium citrate	1 ounce
Tr. of Hyoscyamus	3 fluid drachms

Syrup of tolu;- a sufficient quantity to make 3 fluid ounces.

Directions: One teaspoonful every two hours.

Mr. Kaemmerer says in a note under this prescription: "In compounding this prescription considerable effervescence takes place owing to the potassium citrate containing an excess of acid."

No trouble whatever was encountered in compounding this prescription, a very slight effervescence took place but this would also occur if potassium bicarbonate were shaken or triturated in water.

Potassium citrate was added to a solution of potassium bicarbonate and no appreciable effervescence occurred. Tincture of hyoscyamus and syrup of tolu did not cause any effervervescence with potassium bicarbonate. Syrup of tolu if in good condition is neutral for in its preparation magnesium carbonate is used as a clarifying agent and if any free acids are present in the materials used they will be neutralized by the carbonate. Tr. of hyoscyamus is a neutral slution and potassium citrate if

of U. S. P. purity is alkaline in reaction.

Therefore no appreciable effervescence takes place and the prescription can be easily compounded, the result being a perfect solution.

Prescription No. 4.

Potassium citrate	1 ounce
Ammonium benzoate	4 drachms

Water -- a sufficient quantity to make 4 fl. oz.

Directions: A teaspoonful every three hours.

This prescription does not make a clear solution. When prepared by triturating the salts with the water in a mortar some of the salt does not dissolve and remains in suspension. When prepared by dissolving the salts in hot water crystals separate out upon cooling. The cause of this is that there is not enough water used to dissolve the ammonium benzoate. The potassium citrate prescribed readily goes into solution in the four ounces of water but the ammonium benzoate does not. By using ammonium benzoate alone in the prescription results are obtained similar to those where both ammonium benzoate and potassium citrate are used. Ammonium benzoate is soluble in 10.5 parts of water but here we have less than 8 parts of water. By adding a small amount of ammonia water to the prescription a clear permanent solution results. This is explained by the ready solubility of benzoic acid in solutions of alkali hydroxides. It

dissolves forming benzoates which are held in solution by the excess of alkali present. In this case the benzoate is already present and it only requires the addition of a small excess of alkali to hold that amount in solution which the water itself will not dissolve.

A solution of 4 drachms of ammonium benzoate in 4 ounces of hot water required 22 drops of ammonia water to make it neutral to litmus. There must therefore have been considerable free benzoic acid in the ammonium benzoate and this is readily accounted for by the fact that the ammonium salts of weak organic acids lose ammonia upon exposure to the air. Upon cooling, partial precipitation occurred in this neutral solution and the addition of two drops of ammonia water was necessary to redissolve the precipitate to form a permanent clear solution.

The incompatability in this prescription is largedue to the presence of considerable amounts of free benzoic acid in commercial ammonium benzoate, and partly due to the excessive amount of this salt prescribed. Both can be remedied by the addition of a small amount of ammonia water, a very slight excess only being required.

Prescription No. 5.

Salicylic acid	3 drachms
Potassium acetate	4 drachms
Glycerine	1 fl. ounce
Water	4 fl. ounces.

Directions: One teaspoonful four times a day.

"Quite contrary to what one would expect this makes a perfectly clear solution without any difficulty."

The explanation of this behavior is in the fact that the solutions of alkali acetates have the power of dissolving considerable salicylic acid. R. Rother, in an article published in the American Journal of Pharmacy of 1886, says: "With acetic acid alone salicylic acid is precipitated. It is abundantly soluble in potassium acetate but there must be an excess of potassium acetate present to prevent precipitation by the free acetic acid which is liberated. Three molecules of the acetate to two molecules of salicylic acid gives the right proportion and the following reaction shows that there must be present one molecule of potassium acetate to hold in solution the two molecules of potassium salicylate

formed in the presence of the acetic acid also formed.*"

$$3KC_2H_3O_2 + 2HC_7H_5O_3 = 2KC_7H_5O_3 + KC_2H_3O_2 + 2HC_2H_3O_2.$$
$$3 \times 97.44 \quad 2 \times 137$$

By using the following proportion the amount of potassium acetate required to hold the 3 drachms of salicylic acid in this prescription in solution is considerable less than 4 drachms, the amount prescribed.

$$274 : 292.32 :: 3 : x, \qquad x = 3.2 \text{ drachms.}$$

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* Am. Jour. Pharm., 1886, p. 420.

Salicylic acid and monad salts. R. Rother.

Prescription No. 6.

Quinine sulphate 3 drachms

Dilute sulphuric acid sufficient to dissolve

Sodium salicylate 4 drachms

Extract of malt, a sufficient quantity to make 12 fluid ounces.

Directions: One teaspoonful three or four times a day.

As salicylic acid is precipitated from sodium salicylate by suplhuric acid a precipitate of free salicylic acid acid occurs in this prescription when compounded as written. The object of adding the sulphuric acid is doubtless to increase the solubility of the quinine. The bisulphate is formed and this salt is readily soluble while the sulphate is only soluble in dilute solution.

In compounding this prescription it is best to omit the sulphuric acid entirely. Extract of malt is a thick syrupy liquid and the quinine sulphate can be intimately suspended in it by trituration. The sodium salicylate is freely soluble and will go into solution readily. It is better to have the quinine in suspension anyway because it is less bitter when in an insoluble condition.

Prescription No. 7.

Salicylic acid	2 drachms
Sol. of ammon. acet.	2 fl: oz.
Sp. nitrous ether	1/2 fl. oz.
Syrup	1/2 fl. oz.

Directions: Two teaspoonfuls every three hours until relieved.

According to Mr. Kaemmerer, this prescription was compounded in the following manner.

The salicylic acid was mixed with the solution of ammonium acetate and filtered. The spirit of nitrous ether and the syrup were then added. The reason given for filtration of the mixture of salicylic acid and solution of ammonium acetate was that not all of the salicylic acid had gone into solution and he thought it better to dispense a clear solution. He says that salicylic acid is incompatabile with spirit of nitrous ether but no harmful compound results.

It is quite evident that the basis of this prescription is salicylic acid. As salicylic acid is soluble in water only to the extent of 1 part in 308 parts, it is difficult to prepare an aqueous solution which

will contain in one or two fluid drachms, a full dose of this substance. Many substances have been used to increase its solubility in water, viz.; phosphates, citrates and acetates of the alkalies, borax, and spirit of nitrous ether. This explains the use of solution of ammonium acetate and spirit of nitrous ether in this prescription. There is both a pharmaceutical and chemical incompatability encountered here, the first with regard to solubility of salicylic acid and the other between salicylic acid and spirit of nitrous ether. The question of solubility will first be discussed.

Of the alkaline salts used for the purpose of aiding the solution of salicylic acid in water, those of ammoniua are the most effective. In these cases, the alkaline salicylates are formed and as ammonium salicylate is more easily decomposed than potassium or sodium salicylate, it more closely resembles salicylic acid, therapeutically, than they do. The ammonium compounds will dissolve as much salicylic acid as the potassium salt will, and more than the sodium salts will. In preparing a solution of salicylic acid in alkaline acetate, double decomposition takes place with the formation of alkaline salicylate and free acetic acid.* Salicylic acid is precipitated by acetic acid so it is necessary to have

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* Am. Jour. Pharm., 1886, p. 420.

present an excess of alkaline acetate to hold the salicylate in solution. As shown by R. Rother,* the amount of alkaline salt necessary to produce a permanent solution of salicylic acid is in accordance with the following reaction in which the ammonium salt is used. Three molecules of ammonium acetate are required for two molecules of salicylic acid.

$$3NH_4C_2H3O_2 + 2HC_7H5O_3 = 2NH_4C_7H_5O_3 + NH_4C_2H_3O_2 = 2HC_7H_5O_3.$$

229.63 X 274.02

274.02 parts of salicylic acid require, to form a permanent solution, 229.63 parts of ammonium acetate. Liquor ammonia acetatis (U. S. P.) contains 7% of ammonium acetate. The weight of an ounce of this solution is practically the same as that of water which is 456.4 grains. The weight of two ounces then will be 2 X 456.4 = 912.8 grains. 7% of this is (912.8 X .07) 63.9 grains, the amount of ammonium acetate in the solution.

274.02 : 229.63 :: x : 63.9 x = 76.25 grains,

the amount of salicylic acid which will be held in solution by the ammonium acetate in this prescription. One ounce of spirit of nitrous ether will dissolve 16 grains of salicylic acid to form a solution which can be diluted with water without causing precipitation.**

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* Am. Jour. Pharm., 1886, p. 420.
** Am. Drug. Circ., 1877, p. 130.

One half ounce will dissolve 8 grains. Then 76.25 + 8 = 84.25 grains of salicylic acid which will be held in solution in this prescription. As 120 grains are prescribed there will be 35.75 grains which cannot stay in solution. Below are given the results of careful experiments on this prescription.

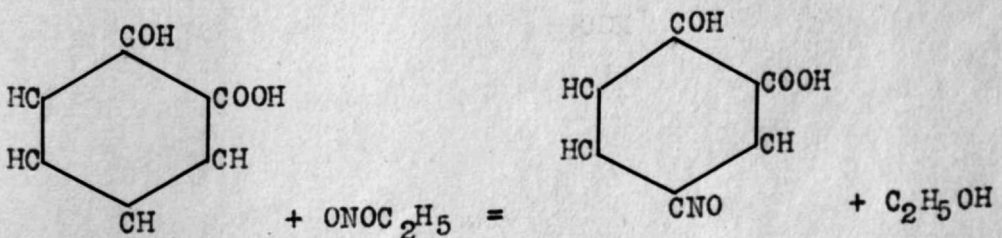
At the room temperature a large part of the salicylic acid would not go into solution in the solution of ammonium acetate and it was necessary to boil the mixture to effect solution. This gave a colorless solution from which upon cooling salicylic acid precipitated. By adding the spirits of nitrous ether and syrup to the solution while hot a light brown color was immediately formed which changed rapidly to a dark red color. Effervescence took place and a nitrous odor was evolved. Upon standing over night a mass of crystals was deposited. They were recrystallized from hot water and when dry were weighed. They weighed 35 grains which perfectly agrees with the computation above given. The melting point was also determined and found to be 156°-157°, which is the melting point of salicylic acid. When 84 instead of 120 grains of salicylic acid were used, no precipitation occurred though the same colored solution resulted.

The chemical incompatability between salicylic acid and spirit of nitrous ether is very apparent as it is

this which causes the coloration of the solution. These color reactions of salicylic acid, and other compounds having the benzene ring, are well known and in many cases are a means of identification.* The chemistry of these color reactions has never been studied to any extent, yet it is probable that in this case the compound formed is a nitroso-salicylic acid, as nitroso-resorcinol, a compound perfectly analogous in every respect, is prepared in a similar manner by the use of amyl nitrite and resorcin.

No nitroso-salicylic acids are known but within the last few years many nitroso- and nitro compounds have been found to be identical and so if this compound were thoroughly studied it might be identified as a nitro-salicylic acid.

The following reaction shows the formation of nitroso-salicylic acid from salicylic acid and ethyl nitrite though the ammonium acetate might also enter the reaction. However the reaction takes place without ammonium acetate and with free salicylic acid as well as its salts.



* Am. Drug. Circ., 1888, p. 273.
Tests & Reagents, Cohn, p. 115.
Proc. A. Ph. A., 47, p. 719.

The reaction takes place slowly in cold but rapidly in hot solution. As Mr. Kaemmerer says, this compound is not harmful, and might even be advantageous if the action of hyponitrous acid is desired by the physician, for undoubtedly the acids of the stomach liberate this compound as well free salicylic acid. This incompatability however is, in all probability not intentional with the physician, his object being to prescribe a mixture containing sufficient salicylic acid so that two fluid drachms will contain a moderate dose. The chemical incompatability alone should prohibit its being dispensed. However if it were not for the excessive amount of salicylic acid prescribed, it might not be noticed as the color only slowly forms when the substances are mixed in cold solution. It is more probable however that heat would be used to facilitate solution of the salicylic acid, and then upon addition of the spirit of nitrous ether the color would be immediately produced.

A simple remedy which would do away with both incompatabilities at the same time is to substitute more solution of ammonium acetate for the spirit of nitrous ether and syrup. This would give a clear permanent solution containing the amount of salicylic acid prescribed. In cases where a smaller percentage of salicylic acid is prescribed the substitution of alcohol for the spirit of ni-

trous ether would also yield a clear solution.

Prescription No. 8.

Tincture of chloride of iron	1 fl. oz.
Dilute phosphoric acid	2 fl. ozs.
Glycerine	2 fl. ozs.

100% solution of sodium phosphate, a sufficient quantity to make 8 fl. ozs.

Directions: A teaspoonful in a half a glass of water after each meal.

Tincture of chloride of iron and phosphoric acid form a perfectly clear solution, the phosphate of iron formed being held in solution by the hydrochloric acid also formed.

$$FeCl_3 + H_3PO_4 = FePO_4 + 3HCl.$$

Glycerine can also be added without any precipitation occurring but when the solution of sodium phosphate is added a precipitation of ferric phosphate immediately occurs. The sodium phosphate binds the hydrochloric acid with the liberation of phosphoric acid and as ferric phosphate is not soluble in phosphoric acid it is precipitated. However, as the precipitate is gelatinous and is readily suspended in the liquid, forming a creamy mixture, there can be no objection to dispensing it in this condition.

The term 100% solution of sodium phosphate is one which might cause a good deal of trouble to pharmacists if this prescription should be presented to pharmacists not acquainted with the physician by whome it was written. As it is written, it can mean nothing but absolutely pure sodium phosphate which of course could not be a solution unless in a fused condition. It may be interpreted to mean one of two things, a 10% solution of sodium phosphate or a saturated solution of sodium phosphate. The first could be assumed by thinking that the physician, intending to write 10, absentmindedly added another cipher making it read 100. The second explanation is one which would be made by the average pharmacist, as there is on the market a saturated solution of sodium phosphate which is frequently prescribed. The physician, in wishing to be sure to get the concentrated solution, might call it a 100% solution, meaning the maximum amount of sodium phosphate soluble in water. In either case the results are similar, the mixture being thicker when the concentrated solution of sodium phosphate is used.

Prescription No. 9.

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Morphine sulphate 3 grains

Potassium cyanide 4 grains

Aromatic sulphuric acid 2 1/2 drachms

Syrup of wild cherry, - a sufficient quantity to make 4 fl. ozs.

Directions: A teaspoonful three times a day.

In this prescription there will undoubtedly be a chemical reaction between the potassium cyanide and aromatic sulphuric acid with the formation of hydrocyanic acid but as the hydrocyanic acid so liberated remains in solution this cannot be called an incompatability. The dose of potassium cyanide is nearly the maximum dose and in connection with the morphine also present might be considered excessive, but doubtless the dose is goverened by a condition of the patient making it entirely permissable.

Prescription No. 10.

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Ammonium iodide	1 drachm
Apomorphine	1 grain
Dilute hydrochloric acid	10 minims
Syrup of liccrice	1 fl. oz.
Peppermint water	2 fl. ozs.

Directions: One teaspoonful every three or four hours.

The main trouble in this prescription is due to the syrup of liccrice. Liccrice preparations are invariably alkaline, ammonia water being used to form a soluble compound with the glycyrrhizic acid which is the active principle. As there is no syrup of licorice official in the U. P. Pharmacopoeia, this may be made by different methods and of different strengths. If there is enough ammonia in the syrup of liccrice to neutralize the hydrochloric acid prescribed, the apomorphine will not go into solution and the prescription should not be dispensed, as there would be great danger of taking an over dose of apomorphine in the last portions of the mixture. On the other hand, if there is not enough ammonia present to neutralize all of the hydrochloric acid, the glycyrrhizic acid will be precipitated and the remaining hydrochloric acid will combine with the apomorphine until it is all

converted into the hydrochloride which will go into solution. Any excess of the acid will react with the ammonium iodide liberating hydriodic acid which, upon standing exposed to light, decomposes with the formation of iodine which will precipitate the apomorphine. By the following reactions it is seen that only a small portion of the hydrochloric acid prescribed is required to convert the apomorphine into apomorphine hydrochloride.

$$C_{17}H_{17}NO_2 + HCl = C_{17}H_{17}NO_2.HCl$$
$$256.16 \quad 36.18 \quad 292.34$$

256.16 : 36.18 :: 1 : x x = 0.1364 grains of hydrochloric acid which combines with one grain of apomorphine. Dilute hydrochloric acid contains 10% of HCl which, for 10 minims, is one grain.

1 - 0.1364 = 0.8636 grains of HCl in excess. Under the foregoing condition a precipitation of either glycyrrhizic acid, apomorphine, or both is very liable to occur. A precipitation of glycyrrhizic acid would cause no serious consequences as it is simply the flavoring agent but as before stated as precipitation of apomorhine might cause serious consequences.

There are two ways in which this prescription can be correctly compounded. First, an equivalent amount of apomorphine hydrochloride should be used in place of the alkaloid apomorphine, and the hydrochloric acid ommitted.

This removes all chance of an excess of acid being present. The amount may be calculated from the molecular weights in the reaction previously given; 292.34 grains of apomorphine hydrochloride are equivalent to 256.16 grains of apomorphine.

292.34 : 356.16 :: x : 1 x = 1.14 grains of apomorphine hydrochloride equivalent to 1 grain of apomorphine. The syrup of licorice used must then be carefully neutralized by some weak acid, e.g., acetic acid, and the prescription can be compounded without any trouble. The other method for compounding this prescription is to substitute apomorphine hydrochloride as before but substitute simple syrup or some other neutral syrup for the syrup of licorice.

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