

5. Of the effects studied, only those upon circulation and temperature appear to be of therapeutic significance.
6. Our observations do not justify claims of diuretic activity for this preparation.
7. A very safe latitude of therapeutic action has been shown.
8. Lethal doses, intravenously or orally, produce a respiratory death.
9. Since this preparation shows the typical nitrite action, the information provided in authoritative texts regarding methemoglobin production and tolerance development for nitrites as a group, should necessarily be born in mind by the physicians employing this preparation.
10. The p_H values were found to change greatly during deterioration, first showing an early trend toward greater acidity, then changing toward neutrality to a much greater degree. No practical significance is attached to these observations, since it would be impossible to control this factor.
11. Owing to the importance of the high alcohol content relative to the stability of this spirit, prescribing this preparation in any aqueous mixture is to be condemned.

A SUGGESTION.

Since Spirit of Ethyl Nitrite has been shown to possess a therapeutically valuable type of activity, and since it has been definitely established that its lack of stability makes it imperative that it be prepared very near to the time of dispensing, and dispensed in small quantities, we believe that individual small amber-glass ampuls containing the now available ethyl nitrite concentrate, in the amount necessary to make one fluidounce of the spirit, would make it possible to dispense this preparation with its full strength assured.

REFERENCES.

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THE STABILITY OF SOLUTION OF IRON AND AMMONIUM ACETATE U. S. P. X.^{1,2}

BY WILLIAM J. HUSA³ AND GEORGE W. BIRMINGHAM.

INTRODUCTION.

Solution of Iron and Ammonium Acetate, or Basham's Mixture as it is commonly known, though one of the older pharmacopœial preparations, is one which has long been a source of dissatisfaction to physicians and pharmacists. When freshly prepared the solution is a transparent brilliant red liquid and has been referred to as undoubtedly one of the most elegant preparations ever introduced for the administration of iron in dilute solution (1). However, the solution is

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prone to rather rapid deterioration, and after standing for a few weeks usually shows considerable turbidity, and frequently very heavy precipitation. For this reason the U. S. P. X directs that this preparation must not be dispensed unless it has been recently prepared.

It has been the purpose of this investigation to study the factors which influence the decomposition of Solution of Iron and Ammonium Acetate, and to seek possible means of retarding the deterioration.

HISTORICAL REVIEW.

1. *Development of Formula for Basham's Mixture.*—As early as 1831, M. Beral, a French pharmacist, submitted a formula for an "Acétate d'ammoniaque et de fer liquide," or "esprit de menderéus ferré" (2). Toward the middle of the nineteenth century, Dr. William Richard Basham of London recommended a combination of tincture of iron chloride with solution of ammonium acetate and acetic acid as highly beneficial in cases of dropsy, a few drops of the tincture according to the age of the patient being added to a drachm of the Liquor Ammonii Acetatis previously acidulated with acetic acid (3). Apparently Basham's Mixture has never had very wide-spread usage in England and it is not official in the British Pharmacopœia.

The following formula, reprinted from the Pharmacopœia of the Philadelphia Hospital in the *American Journal of Pharmacy* for March 1876, was the first formula given for Basham's Mixture in an American journal: "Liquoris ammonii acetatis $f\text{ʒ}ij$, Tincturæ ferri chloridi $f\text{ʒ}ijss$, Acidi acetici diluti $f\text{ʒ}j$, Curacoa, vel alcohol $f\text{ʒ}ij$, Syrupi, Aquæ aa $q. s. ad f\text{ʒ}vj$." However, a report (4) to the AMERICAN PHARMACEUTICAL ASSOCIATION in 1901 gave the following, from a revised edition of the Pharmacopœia of the Philadelphia Hospital, with the notation that it was believed to have been the original formula of Dr. Basham: "Tincture of ferric chloride 0.6 cc., diluted acetic acid 1.0 cc., solution of ammonium acetate 8.0 cc., elixir of orange 2.0 cc., glycerin 2.0 cc., water, $q. s. 15.0 cc.$ " In this formula, the quantity of the tincture was slightly reduced and the acetic acid increased. Many variations of the formula were in use in this country prior to the admittance of the solution to the U. S. P. of 1880. J. T. Shinn (5) in 1876 reported at a meeting of the Philadelphia College of Pharmacy that he had found Basham's Mixture prescribed, and that there was a difference in the recipe as obtained from different sources. The statement was made that twenty minims of the tincture and one fluidounce of solution of ammonium acetate were the correct proportions, though no other ingredients of a working formula were given.

The remedy having attained much popularity, and as there was some doubt as to the proper proportion of ingredients, Wiegand (6) in 1887 submitted a formula for Basham's Mixture containing tincture of ferric chloride 3 parts, diluted acetic acid 4 parts, solution of ammonium acetate 32 parts, curacoa 8 parts, syrup of orange peel 12 parts, and water sufficient to make 64 parts. This formula he stated had been given him by a Charles Bullock who he believed had copied it from an English journal (3).

However, a few years later when the solution appeared as official in the U. S. P. of 1880, this formula was changed slightly by the replacement of curacoa and syrup of orange peel by elixir of orange and simple syrup, the change being made, as was suggested by Hausmann (7), because of a deep brown almost black color given to the preparation by the syrup of orange peel. The strength in active ingredients was cut down to almost half what had formerly been recommended, the formula being as follows: "Tincture of chloride of iron 2 parts, diluted acetic acid 3 parts, solution of acetate of ammonium 20 parts, elixir of orange 10 parts, syrup 15 parts, water 50 parts, to make 100 parts."

The title of Basham's Mixture as it was given in the U. S. P. of 1880 was "Mistura Ferri et Ammonii Acetatis." The Dispensatory (1) at that time made the comment that the title was unfortunate in that this was not a mixture from a pharmaceutical point of view, but a transparent bright red liquid in which all the ingredients were in perfect solution, hence it was properly a Liquor. In accordance with this view the 1890 pharmacopœial title was changed to "Liquor Ferri et Ammonii Acetatis." In 1887 the *Druggists Circular* had published a suggestion, made by H. R. LeValley, that the syrup of the official formula be replaced by glycerin, reporting that a solution so made had remained free from precipitation after standing thirty-five days (8). Accordingly, twelve per cent by volume of glycerin was added to the official formula at that time.

At the same time the newly official aromatic elixir replaced the elixir of orange, leading to the following formula: "Tincture of ferric chloride 20 cc., diluted acetic acid 30 cc., solution of ammonium acetate 200 cc., aromatic elixir 100 cc., glycerin 120 cc., water, a sufficient quantity to make 1000 cc."

The first official formulas for Basham's Mixture (those of the U. S. P. of 1880 and 1890) were radical departures from the formulas originally used and upon which the reputation of the preparation was first established, in that the quantities of the active ingredients were cut down about half. Concerning this J. W. England (3) wrote, "In an attempt to secure pharmaceutical elegance and permanency of product, therapeutical efficiency has been sacrificed or largely nullified." Haussmann (7) reported in 1891 that from a medical point of view the slight amount of active ingredients in the official formula was objectionable. For that reason, he said, many physicians prescribed it in extemporaneous solution, while others specified "old formula," referring to a modification printed in the U. S. Dispensatory at that time which was nearly three times the iron strength of the official formula. To meet these objections the U. S. P. of 1900 brought the amounts of tincture of ferric chloride and of solution of ammonium acetate up to four per cent and fifty per cent by volume, respectively, as compared with two and twenty per cent in the earlier official formula. At the same time the volume of aromatic elixir was brought up to twelve per cent, thus making the formula: "Tincture of ferric chloride 40 cc., diluted acetic acid 60 cc., solution of ammonium acetate 500 cc., aromatic elixir 120 cc., glycerin 120 cc., distilled water, a sufficient quantity to make 1000 cc." This formula has not been changed in succeeding revisions up to the present.

In Basham's Mixture ferric acetate in some form—probably a basic acetate as suggested by Weinland (9) (10)—is produced. The presence of ammonium acetate in great excess is a valuable factor therapeutically, since it is held that much of the good achieved from the use of this preparation in kidney disorders depends on the diuretic properties of the ammonium acetate (11). The aromatic elixir is present chiefly as an adjuvant, while the glycerin serves mainly to stabilize the preparation to a certain extent.

2. Chemical Composition and Deterioration of Solutions of Ferric Salts.—

The changes which occur in aqueous solutions of ferric salts have long been known and attributed to hydrolysis. The change is progressive, depending on the natural stability of the particular salt, and on such conditions as dilution, temperature, etc. Conditions which increase the hydrolysis of ferric salts at first deepen the color to a clear but intense red, and finally precipitate ferric hydroxide (12). The primary darkening is generally attributed to the formation of colloidal ferric hydroxide, or a highly hydrated oxide (13), after which the particles agglomerate and come down as a heavy precipitate.

The mechanism of the deterioration of solutions of ferric salts has been studied from time to time. Kruke (14) in 1871 believed that the process could be separated into two stages, *first*, a darkening due to formation of soluble ferric oxide (Graham's oxide) and free HCl, and *second*, a turbidity and deposition, according to concentration and temperature, of either difficultly soluble ferric oxide (Pean's), ferric oxychloride or dense anhydrous ferric oxide. Kruke concluded that in solutions of ferric chloride the amount of decomposition increases with rise in temperature and that stability toward heat decreases on dilution. Antony and Gigli (15) after studying the reaction quantitatively concluded that ferric chloride is hydrolyzed in three stages giving $\text{FeCl}_2(\text{OH})$, $\text{FeCl}(\text{OH})_2$ and $\text{Fe}(\text{OH})_3$. Pux-eddu (16) in 1923, after certain conductivity and thermochemical measurements, was led to conclude that the changes were even more complex than had heretofore been indicated. In general, however, the solutions of ferric salts do not hydrolyze to the extent of actual precipitation under ordinary conditions of temperature.

Tian (17) explains this on the ground that while the colloidal particles tend to form particles of larger size, an equilibrium is established owing to chemical forces tending to increase dispersity.

All ferric salts in solution undergo the same or a similar type of hydrolytic change as has been shown to be true of ferric chloride, though the hydrolysis is most apparent in the salts of the weaker acids. Thus ferric acetate is one of the most extensively hydrolyzed and consequently one of the least stable of the ferric salts, showing very rapid hydrolysis especially in dilute solutions, even at room temperature. The feebleness of the union of ferric acetate was first pointed out by Pean de St. Gilles (18). It was further shown by Berthelot (19) that a few minutes of boiling effected almost complete disunion of the acid and base followed by a molecular coagulation or condensation after which precipitation occurred.

The dark red color of ferric acetate solutions has generally been attributed to the undissociated molecules (20). Weinland and Gussmann (10), however, state that it has not been found possible to prepare the tri-acetate of iron, and that the red color is due to a mono-acetate of a base, having the formula $[\text{Fe}_3(\text{CH}_3\text{COO})_6(\text{OH})_2] \cdot \text{CH}_3\text{COO}$. They showed that the precipitate obtained on boiling a solution containing ferric chloride and sodium acetate corresponds approximately with the composition $\text{Fe}_3(\text{CH}_3\text{COO})(\text{OH})_2\text{O}_3$. It would appear that the deep red color is due to the presence of a product of hydrolysis in colloidal suspension, since Hammett (12) explains that the addition of the acetate ion to ferric salt solutions produces the same deep red color as do other methods of increasing hydrolysis. Thus a dialyzed solution of colloidal ferric hydroxide shows approximately the same color as Basham's Mixture.

3. *Deterioration of Basham's Mixture.*—It can readily be seen that in such a dilute solution of ferric acetate as Basham's Mixture the hydrolysis will be very rapid. Graff (21) in 1894 suggested that the addition of a few drops of 36% acetic acid to the solution of ammonium acetate before adding the excess of acid directed by the U. S. P. would insure much greater stability of the solution. He also suggested that the heat developed in adding the alcoholic tincture of ferric chloride to the aqueous ammonium acetate solution possibly hastens formation of the basic acetate of iron, and that this might be avoided by first diluting the tincture with an equal volume of water and allowing to cool before adding it in its regular order. Haussmann (7) also suggested that increasing the amount of acetic acid was perhaps the only remedy against the instability of the solution. However, a too great excess of acid is objectionable from the standpoint of palatability.

The relation of acidity and alkalinity to the stability of this preparation is of special interest in the light of certain research dealing with the colloidal nature of the "scale preparations" of iron (iron and ammonium citrate, iron and ammonium tartrate, etc.), solutions of which bear marked similarity to Basham's Mixture. Graham (22) in 1862 observed that ferric hydroxide is readily peptized in alkaline solutions of organic hydroxy compounds. Hakomari (23) concluded from certain conductivity, dialysis and ultra-microscopic measurements that the non-precipitability of iron in hydroxy-acid solutions is due partly to formation of a complex between the iron and the hydroxy-acid. Bancroft (24) and Bachman (25), who investigated products from adding sodium hydroxide to iron solutions in presence

of glycerol, sucrose and other non-dissociating hydroxy compounds, concluded that the metal is present partly as a colloid and partly as a crystalloid complex. Morton (26) from results of glass electrode and dialysis measurements observed a definite stability of iron compounds of the "scale salt" type (hydroxy-acid complexes of iron) in alkaline solutions, and concluded that in acid solutions these complexes are present mainly as true electrolytes, but in alkaline solutions they are decomposed to varying extents with the formation of basic hydrosols which are readily peptized and protected by the hydroxy-acid anion. Chatterji and Dhar (27) also showed that ferric hydroxide is peptized by adding sodium hydroxide to solutions of ferric salts in the presence of glycerol or sugar, although these substances will not peptize if added after precipitation has occurred. Todd (28) observed the same thing and reported that samples of iron and ammonium citrate which in aqueous solution are neutral or slightly alkaline remain bright and free from precipitation much longer than do samples which give an acid reaction.

The stability of Basham's Mixture was improved by the replacement of the syrup of the older formula by glycerin, as suggested by LeValley (8). It has been reported (29) that by doubling the amount of glycerin in the official formula, solutions have been prepared which have kept perfectly clear for a period of over eighteen months exposed to ordinary conditions of diffused light. Dunning (30) reported on a formula for Basham's Mixture in which the amount of glycerin was increased from 12 to 20 per cent by volume, which remained without change for more than a year.

Krantz (31) concluded that the superior preserving power of glycerin over an equal weight of sugar in Basham's Mixture is due to the higher molecular concentration of the former, with resulting greater protection against collision and reaction of the hydroxyl ions of water with the ferric acetate molecules.

EXPERIMENTAL PART.

Materials Used.—The U. S. P. X requires that ammonium carbonate shall yield not less than 30% and not more than 32% of NH_3 . The samples used in the present investigation were assayed by the U. S. P. method; the NH_3 content ranged between 31.87 and 32.00%. Solution of Ammonium Acetate was made by one of the alternative processes, *i. e.*, by dissolving ammonium carbonate in diluted acetic acid, the latter being adjusted to 6.0%. The strength of Solution of Ferric Chloride was checked by specific gravity determinations. Both the solution and the tincture of ferric chloride were freshly prepared for each experiment, to overcome the difficulty of various degrees of hydrolysis in solutions of different ages.

General Methods.—The solutions were exposed under various conditions, 50-cc. portions in 2-oz. prescription bottles being placed in direct sunlight on the roof, in diffused light at room temperature and in darkness at room temperature. An accelerated aging test was carried out by placing bottles of the various solutions in a constant temperature oven, using temperatures specified in the tables which follow. An aging test of this character was used by Thomas and Hamburger (32) in testing the stability of ferric oxybromide hydrosols.

The solutions on exposure were examined daily, and the time of decomposition recorded was that which elapsed before the formation of a characteristic dense

precipitate. Instances in which only discoloration of the solution, turbidity or precipitation of a special type were found have been specially noted. In all experiments the stability of the modified solution was compared with that of a control which was exactly U. S. P. in every respect and prepared at the same time that the particular experiment was being carried out.

Effect of Colored Bottles.—A test was carried out in which U. S. P. Basham's Mixture in glass bottles of different colors was exposed under various conditions.

TABLE I.—DECOMPOSITION OF BASHAM'S MIXTURE IN VARIOUS COLORED GLASS BOTTLES UNDER VARIOUS CONDITIONS.

Color of Bottle.	Days after Which Precipitation Was Observed.		
	Sunlight.	Diffused Light.	Dark.
Colorless	6	18	20
Green	6	18	20
Brown	14	20	20
Black	23	23	23

Table I indicates that the solution is most stable in black bottles, less stable in amber-colored bottles and least stable in colorless or greenish bottles. In black bottles the stability was uniform under all conditions of exposure tested, while the other bottles offered less protection against the decomposing effect of sunlight.

Effect of Varying Individual Ingredients.—Experiments were carried out to determine the effect of varying the amounts of the individual ingredients one at a time.

TABLE II.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF GLYCERIN (OTHER INGREDIENTS PRESENT IN U. S. P. PERCENTAGE).

Glycerin, %	Minutes. Oven, 90° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	20	1	1	1
2	40	1	1	1
5	40	1	1	1
8	40	2	4	4
12 (U. S. P.)	50	6	18	21
18	50	8	23	24
24	70	15	*	*

* No precipitation after 103 days.

Table II shows the importance of having at least the U. S. P. proportion of glycerin in the formula and indicates that an increase in the percentage of glycerin gives a more stable solution.

TABLE III.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF ELIXIR (OTHER INGREDIENTS PRESENT IN U. S. P. PERCENTAGE).

Aromatic Elixir, %	Minutes. Oven, 90° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	50	1	4	4
2	50	4	10	12
5	50	4	10	12
8	50	5	15	18
12 (U. S. P.)	50	6	18	21
18	60	6	25	24
24	40	6	18	23

Stability of the solution increases with the amount of aromatic elixir in the formula up to a certain point, 18 per cent giving the greatest stability.

TABLE IV.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF ACETIC ACID (OTHER INGREDIENTS PRESENT IN U. S. P. PERCENTAGE).

Diluted Acetic Acid, %.	Minutes. Oven, 90° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	50	6	78 (Slight)	78 (Slight)
2	50	6	15	16
4	50	6	18	21
6 (U. S. P.)	50	6	18	21
8	35	1*	4*	4*
12	35	1*	4*	4*
18	35	1*	4*	4*

* Light precipitate which redissolved on shaking.

Table IV indicates that the stability of the solution in diffused light and darkness is greatly increased by leaving out the diluted acetic acid.

TABLE V.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF FERRIC CHLORIDE (OTHER INGREDIENTS PRESENT IN U. S. P. PERCENTAGE).

Tincture of Ferric Chloride, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
4 (U. S. P.)	105	6	14	17
8	120	7	16	19
12	120	9	20	22

The stability of the solution increases slightly as the percentage of tincture of ferric chloride increases.

Effect of Various Ingredients in Absence of Others.—To further determine the effect that the individual ingredients have upon the stability of the solution, samples were prepared in which only the quantities of the tincture of ferric chloride and solution of ammonium acetate were kept at the U. S. P. percentage. In this

TABLE VI.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF SOLUTION OF AMMONIUM ACETATE (DILUTED ACETIC ACID, AROMATIC ELIXIR AND GLYCERIN OMITTED).

Solution of Ammonium Acetate, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	*	*	*	*
2	*	*	*	*
4	*	*	*	•
6	*	*	*	*
10	*	*	*	*
25	45	1	1	1
40	45	1	1	1
50	45	1	1	1
60	30	1	1	1
70	30	1	1	1
80	30	1	1	1
Control (U. S. P. formula)	70	6	15	18

* No precipitation after 81 days.

way the effect of the different ingredients independent of the presence of other substances was tested by varying the percentages in the aqueous ferric acetate solutions. A preliminary experiment was run by varying the proportions of solution of ammonium acetate added to the U. S. P. quantity of tincture of ferric chloride.

In absence of stabilizing ingredients, 10% of solution of ammonium acetate does not cause precipitation but 25% or more causes precipitation.

TABLE VII.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF DILUTED ACETIC ACID (AROMATIC ELIXIR AND GLYCERIN OMITTED).

Diluted Acetic Acid, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	40	1	1	1
2	40	2	1	1
4	40	2	1	1
6	40	2	2	2
10	40	2	2	3
25	70	3	7	9
Control (U. S. P. formula)	100	6	22	29

In absence of aromatic elixir and glycerin the stability increases with increasing percentage of diluted acetic acid, but even with 25% of diluted acetic acid the solution is much less stable than the U. S. P. formula.

TABLE VIII.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF AROMATIC ELIXIR (DILUTED ACETIC ACID AND GLYCERIN OMITTED).

Aromatic Elixir, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	45	1	1	1
2	45	1	1	1
4	45	1	1	1
6	45	1	1	1
10	45	1	1	1
25	55	1	3	3
40	55	1	7	10
Control (U. S. P. formula)	70	6	15	18

In absence of glycerin and diluted acetic acid, solutions of even a high percentage of aromatic elixir are not as stable as the U. S. P. formula.

TABLE IX.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF GLYCERIN (DILUTED ACETIC ACID AND AROMATIC ELIXIR OMITTED).

Glycerin, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark.
0	30	1	1	1
2	30	1	3	3
4	55	1	7	10
6	60	2	12	15
10	60	4	27	29
25	180	11	*	*
40	360	27	*	*
Control (U. S. P. formula)	75	6	15	18

* No precipitation after 81 days.

In absence of diluted acetic acid and aromatic elixir, the solution with 10% glycerin (less than U. S. P.) is more stable in diffused light and darkness than the solution of the U. S. P. formula; stability increases with the amount of glycerin.

Effect of Addition of Alkali.—Tests were made in which diluted acetic acid was omitted and small amounts of NaOH added at a point following the mixing of the solution of ammonium acetate and tincture of ferric chloride. Under ordinary conditions of storage these were more stable than the U. S. P. formula. Likewise the addition of sodium acetate appeared to increase the stability. Since the greater stability of the less acid solutions under ordinary conditions seemingly refutes the long prevalent idea that slight increases in the acidity of Basham's Mixture improve the stability, further work is in progress on this point.

Effect of Sucrose.—The effect of sucrose on the stability of the solution was tested in one series of experiments in which varying percentages were added to solutions made U. S. P. in respect to ferric chloride and ammonium acetate content, the other ingredients of the U. S. P. formula being omitted. Another series of tests was made in which the sugar was added to the regular U. S. P. formula. In both cases the sugar was added to the solution of ammonium acetate before the tincture of ferric chloride was added, and as much of it as possible put into solution before making the other additions.

TABLE X.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF SUCROSE (DILUTED ACETIC ACID, AROMATIC ELIXIR AND GLYCERIN OMITTED).

Sucrose, %.	Minutes. Oven, 75° C.	Time after Which Precipitation Was Observed.		
		Sunlight.	Days. Diffused Light.	Dark:
0	45	1	1	2
2	45	1	1	2
4	45	1	2	2
6	45	1	2	3
10	45	1	3	3
25	60	2	3	3
40	60	4	4	4
Control (U. S. P. formula)	75	6	15	18

Table XI indicates that sucrose alone is not effective in stabilizing the solution.

TABLE XI.—DECOMPOSITION OF BASHAM'S MIXTURE CONTAINING VARIED AMOUNTS OF SUCROSE (FORMULA CONFORMS TO U. S. P. IN OTHER RESPECTS).

Sucrose Added, %.	Time after Which Precipitation Was Observed.	
	Sunlight.	Days. Diffused Light.
0 (U. S. P.)	6	12
2	7	13
4	7	19
6	7	*
10	8	*
25	10	*
40	20	*
50	33 (slight)	*
60	33 (slight)	*
65	33 (slight)	*

* No precipitation in 42 days.

These experiments suggest that it would be well to consider an increase in the percentage of sucrose in the official formula, *i. e.*, adding some in addition to that present in the aromatic elixir. It is apparent that Basham's Mixture might be prepared in the form of a syrup, which would be more stable and possibly more palatable than the solution. It is interesting to note that a formula for a syrup of this kind was presented many years ago by M. Beral (2), who called his preparation "sirop d'acétate d'ammoniaque et de fer."

Effect of Other Additions.—From the tests carried out thus far it appears that the following tentative conclusions may be drawn. HCl in high concentration retards precipitation, though low concentrations hasten the appearance of a light precipitate. Large quantities of NaCl hasten decomposition, but smaller amounts appear to have a stabilizing effect. NH₄Cl increases the stability in diffused light and darkness. Rochelle salt and sodium citrate have a marked stabilizing influence; the higher percentages of these salts caused discoloration in the solutions stored in sunlight. Protective colloids such as gelatin, agar, acacia and tragacanth were not effective as stabilizers in Basham's Mixture in absence of glycerin, diluted acetic acid and aromatic elixir; when used in addition to the ingredients of the U. S. P. formula there was some increase in stability in the following concentrations: gelatin 1%, agar 0.2%, acacia 1%.

Stability toward Electrolytes.—The stability of colloidal solutions is sometimes considered from the standpoint of precipitation by electrolytes. Since an examination of the tables indicates that the results in the accelerated heat test are not directly proportional to the stability under usual conditions, some attention was devoted to the question of whether the stability of Basham's Mixture toward electrolytes would bear a definite relation to stability under usual conditions of storage. Tests were carried out to determine the minimal precipitating concentrations of Na₂SO₄ and of Na₂HPO₄ for official Basham's Mixture and some of the modified formulas.

TABLE XII.—DECOMPOSITION OF BASHAM'S MIXTURE OF VARIOUS FORMULAS COMPARED WITH STABILITY TOWARD ELECTROLYTES.

Composition.	Minutes. Oven, 75° C.	Time for Precipitation.			Minimal Precipitating Concn. in Millimoles.	
		Sun- light.	Days. Diffused Light.	Dark.	Na ₂ SO ₄ .	Na ₂ HPO ₄ .
U. S. P.	75	6	15	18	7.5	0.04
U. S. P. (dil. acetic acid, glycerin and elixir omitted)	45	1	1	1	4.5	0.005
U. S. P. (dil. acetic acid omitted)	80	6	62	*	5.0	0.035
U. S. P. plus 1% N NaOH	80	6	74	*	5.0	0.030
U. S. P. plus 24% glycerin	180	15	*	*	8.5	0.045

* No precipitation in 90 days.

From the results in Table XII, it appears that the accelerated heat test gives a better indication of the stability under ordinary conditions than does the precipitation test with electrolytes.

SUMMARY.

1. The decomposition of Basham's Mixture is accelerated by light and heat.

2. It is important to have at least the U. S. P. proportion of glycerin in the formula and an increase in the percentage of glycerin gives a more stable solution.

3. Stability of the solution increases with the amount of aromatic elixir in the formula up to a certain point, 18% giving the greatest stability.

4. Under ordinary conditions of storage Basham's Mixture appears to be more stable when the diluted acetic acid is omitted, with or without the addition of small quantities of NaOH or sodium acetate. Further work is in progress on this point.

5. Sucrose in high percentages is an effective stabilizer if used in presence of all the ingredients of the official formula.

6. The stability of the solution is increased slightly by increasing the quantity of tincture of ferric chloride used.

7. The stability of the solution is increased by HCl, NH₄Cl and by small quantities of NaCl, but high concentrations of NaCl hasten precipitation.

8. Rochelle salt and sodium citrate increase the stability of the solution.

9. Certain proportions of gelatin, agar and acacia increase the stability somewhat when used in addition to the ingredients of the U. S. P. formula.

10. An accelerated heat test gives a better indication of the stability under ordinary conditions than does a precipitation test with electrolytes.

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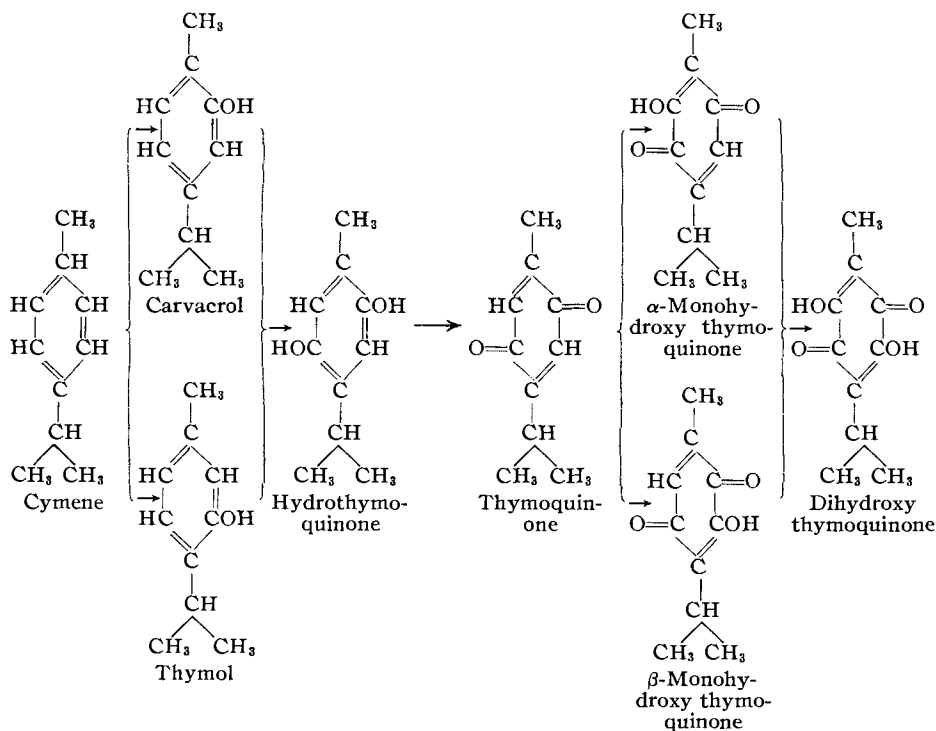
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BROM DERIVATIVES OF HYDROTHYMOQUINONE.*

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In the course of a bactericidal study of oxygenated derivatives of cymene, a striking group has been studied in connection with the phytochemical investigation of various species of the genus *Monarda*. The chemical relationship of its members can readily be understood by a glance at the following structural formulas:



It has been noted that to a certain extent an increase in the hydroxyl content resulted in a corresponding elevation of bactericidal potency (1). In other words,

* Scientific Section, A. PH. A., Toronto meeting, 1932.