TABLE III.—KCl–KI–WATER SYSTEM AT 40° C.

Gm. KCl Added per 100 Cc. KI Solution.	Cc. KIO_3 Used.	Cc. $N/10$ $AgNO_3$ Equivalent to KI from Col. 2.	Gm. KI /100 Cc. Solution.	Cc. $N/10$ $AgNO_3$ Equivalent to Total Halogen.	Gm. KCl/100 Cc. Solution.
0	32.20	16.10	107.2	16.13	..
...	32.20	...	...	...	..
2	31.40	15.72	104.5	16.40	2.04
...	31.40	...	...	...	..
4	30.40	15.20	101.2	16.67	4.39
...	30.35	...	...	...	..
6	29.40	14.70	97.9	16.55	5.55
...	29.40	...	...	...	..
8*	28.85	14.44	96.2	16.94	7.49
10	28.75	14.38	95.7	17.18	8.39
15	28.80	14.38	95.9	16.88	7.49
20	28.80	14.38	95.9	16.94	7.67
25	28.80	14.38	95.9	17.09	8.12
30	28.7	14.28	95.5	17.08	7.88
Average	...	...	95.9	...	7.86

* These data show that with 8 or more grams of KCl per 100 cc. of the KI solution the system is in equilibrium with a solid phase containing both KCl and KI.

TABLE IV.—SOLUBILITY OF KCl.

Temperature, ° C.	Gm. KCl/100 Cc. Solution.
20	29.74
30	31.88
40	33.98

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A STUDY OF FOWLER'S SOLUTION.

BY CHARLES SCHWARTZ, JR.*

The fact that Fowler's Solution is subject to deterioration on standing is well known. Its alkalinity also has proven to be objectionable in the compounding of many medicines. It seems, then, that if the U. S. P. formula could be modified so that the alkalinity would be reduced without causing more rapid decomposition, a more desirable product would result. Since moldy growths often develop in the Solution, the addition of a suitable preservative would also serve to improve it.

The formula of Fowler's Solution as given in the U. S. P. X is as follows:

Arsenic Trioxide	10 Gm.
Potassium Bicarbonate	20 Gm.
Compound Tincture of Lavender	30 cc.
Distilled Water, a sufficient quantity to make	1000 cc.

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Each hundred cubic centimeters must contain the equivalent of not less than 0.975 Gm. and not more than 1.025 Gm. of As_2O_3.

A résumé of the formulas adopted by foreign pharmacopœias is of interest. Chart I represents a comparative study of the principal ones. A study of this chart shows: (1) that in addition to potassium bicarbonate, the hydroxide and carbonate of potassium are also used; (2) that the majority are more or less alcoholic and (3) that the final products are in some cases nearly neutral, while in others, are alkaline to varying degrees.

E. M. Smelt[1] reports an investigation of the keeping properties of the solution adopted by the British Pharmacopœia. The latter solution is of particular interest, in that it is almost neutral in reaction. His findings are that: (1) the addition of preservatives or the proper adjustment of p_H inhibits the growth of molds; (2) the depositing of crystals can be controlled by increasing the alkalinity or acidity, and (3) the use of sodium hydroxide instead of potassium hydroxide encourages rather than prevents the growth of molds.

Although much work has been done on all of these solutions, their diversity in formulas indicates that a product satisfactory in all respects has not yet been attained.

CHART I.

Title.	Arsen. Triox.	Pot. Bicarb.	Pot. Carb.	5% Liq. Pot. Hydrox.	Sp. Lav.	Tr. Lav.	Co. Sp. Balm.	Alcohol.	Acid. Hydrochl. Dil.	Water Sufficient Quantity to Make.
Liquor Potassii Arsenitis U. S. P. 1926	10 Gm.	20 Gm.	....	...	..	30 cc.	....	....	....	1000 cc.
Liquor Arsenicalis B. P. 1932	10 Gm.	....	....	100 cc.	..	...	....	....	±28 cc.	1000 cc.
Liquor Arsenicalis, Fowleri Netherlands P. 1926	10 p.	....	10 p.	...	40 p.	...	...	....	±35 p.	1000 p.
Liquor Kalii Arsenitis Swedish P. 1925	10 Gm.	10 Gm.	....	...	10 cc.	...	....	....	50 cc.	1000 cc.
Liquor Kalii Arsenicosi German P. 1926	10 p.	10 p.	....	...	30 p.	...	....	120 p.	....	1000 p.
Kalium Arsenicosum Solutum Italian P. 1929	10 p.	10 p.	....	...	..	...	....	100 p.	....	1000 p.
Soluté D'Arsénite De Potasse French P. 1908	10 Gm.	....	10 Gm.	...	..	...	30 Gm.	120 Gm. (90%)	....	1000 Gm.

Abbreviation, p. = parts.

EXPERIMENTAL.

In view of the probability that some of the alkali is consumed by the tinctures and spirits commonly added to flavor, color or preserve the solution, it was decided to eliminate such agents, substituting for them alcohol or glycerin, both of which should exert a preservative action. Further, since the bicarbonate, hydroxide and carbonate of potassium have all been used, a comparison of the stabilities of solutions made with each seemed worth while.

Accordingly, twelve solutions were prepared containing varying amounts of the above-named agents. In all cases, the alkali content was reduced below that

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[1] E. M. Smelt, *Quart. J. Pharm. Pharmacol.*, 6 (1933), 375.

officially specified. U. S. P. materials were used throughout, the sample of arsenic trioxide available assaying 99.5%, undried. The solutions, excepting one, were stored in corked bottles of white glass, not completely filled, since this would best duplicate ordinary dispensary conditions. In order to ascertain the effect of storage in well-filled, glass-stoppered bottles, the twelfth was stored in this manner.

The solutions were assayed immediately after preparation and subsequently at ten-day intervals, according to the U. S. P. procedure. A commercial sample which had been carefully stored for an indefinite period in the original corked bottle of amber glass was also assayed to determine, if possible, just how far the decomposition would proceed. The latter solution was the product of a reputable manufacturer and was labeled U. S. P.

CHART II.—FORMULAS USED IN PREPARING THE TWELVE SOLUTIONS.

Ingredients.	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.	No. 6.	No. 7.	No. 8.	No. 9.	No. 10.	No. 11.	No. 12.	No. 13.*
Arsen. Triox.	10 Gm.	10	10	10	10	10	10	10	10	10	10	10	10
Pot. Bicarb.	......	...	7.6	...	...	7.6	...	7.6	5	....	...	...	20
Pot. Hydrox.	......	5	....	...	5	....	...	....	...	3.4	...	...	......
Pot. Carb.	......	...	....	6	...	....	6	....	...	....	4	...	....
Alcohol	......	50 cc.	50	50	...	....	...	30	...	....	50	50	Co. Tr. Lavend. 30 cc.
Glycerin	100 cc.	...	....	...	50	50	50	....	50	50	...	...	....
Dist. Water *q. s.*	1000 cc.	1000	1000	1000	000	1000	1000	1000	1000	1000	1000	1000	1000

* A commercial product labeled U. S. P.; hence the U. S. P. quantities are tabulated.

CHART III.—RESULTS OF ASSAYS MADE EVERY TEN DAYS, EXPRESSED AS GM. OF As_2O_3 PER 100 CC.; ALSO LOSS OF As_2O_3 PER 100 CC. IN GM.

Sol. No.	0 Days.	10 Days.	Total Loss.	20 Days.	Total Loss.	30 Days.	Total Loss.	40 Days.	Total Loss.	50 Days.	Total Loss.	60 Days.	Total Loss.
1	0.989	0.987	0.002	0.979	0.010	0.972	0.017	0.972	0.017	0.972	0.017	0.972	0.017
2	0.998	0.995	0.003	0.991	0.007	0.991	0.007	0.989	0.009	0.989	0.009	0.989	0.009
3	0.998	0.995	0.003	0.991	0.007	0.991	0.007	0.991	0.007	0.991	0.007	0.991	0.007
4	0.989	0.988	0.001	0.986	0.003	0.981	0.008	0.980	0.009	0.980	0.009	0.980	0.009
5	1.001	0.995	0.006	0.995	0.006	0.993	0.008	0.992	0.009	0.991	0.010	0.991	0.010
6	0.998	0.997	0.001	0.994	0.004	0.994	0.004	0.994	0.004	0.994	0.004	0.992	0.006
7	0.997	0.997	0.000	0.994	0.003	0.994	0.003	0.992	0.005	0.992	0.005	0.992	0.005
8	0.998	0.997	0.001	0.991	0.007	0.991	0.007	0.991	0.007	0.991	0.007	0.991	0.007
9	1.002	1.001	0.001	0.993	0.009	0.991	0.011	0.991	0.011	0.991	0.011	0.991	0.011
10	1.002	1.001	0.001	0.992	0.010	0.992	0.010	0.992	0.010	0.992	0.010	0.992	0.010
11	1.004	1.002	0.002	0.994	0.010	0.994	0.010	0.994	0.010	0.992	0.012	0.992	0.012
12	0.993	0.989	0.004	0.984	0.009	0.984	0.009	0.984	0.009	...	...	...	...
13	0.958	0.958	0.000	...	...	...	...	...	...	...	...	...	...

The formulas of the twelve solutions are summarized by Chart II. Equivalent quantities of the alkali salts were used, taking into account the purity rubric as stated in the U. S. P., as follows:

	K_2CO_3.	$KHCO_3$.	KOH.
Molecular weights	138.21	100.11	56.11
Equivalent weights	138.21	200.22	112.22
Assumed amount of water present	15%	negligible	15%
Corrected equivalent weights	162.6	200.22	132.0

Chart III tabulates the results of the assays, together with the loss in trivalent arsenic content in solution. Within the first ten-day period, sedimentation was noted in the two solutions containing no alkali. Whereas the sedimentation was marked in these two solutions over the total period of observation, the amount shown by all of the others was negligible. The commercial product had a crystalline deposit, as well as a small amount of gelatinous residue. None had an unpleasant odor.

DISCUSSION.

The twelve solutions may be divided into two groups according to the total loss of trivalent arsenic within sixty days, as follows:

Group I.

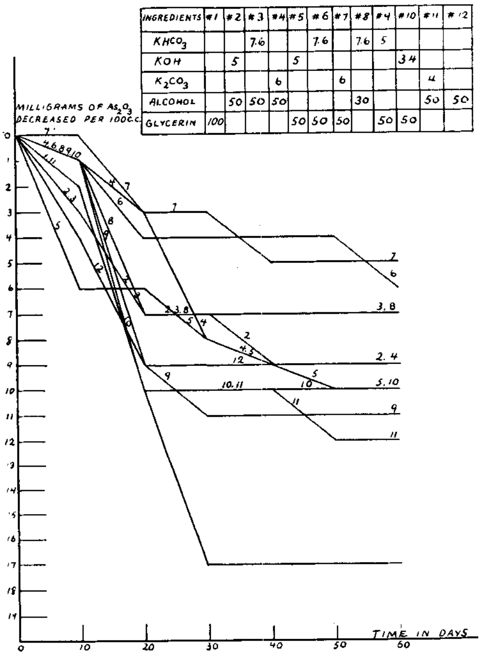
Solution 3—7 mg. decrease As_2O_3 per 100 cc.
Solution 6—6 mg. decrease As_2O_3 per 100 cc.
Solution 7—5 mg. decrease As_2O_3 per 100 cc.
Solution 8—7 mg. decrease AsO_{23} per 100 cc.

Group II.

Solution 1—17 mg. decrease As_2O_3 per 100 cc.
Solution 2— 9 mg. decrease As_2O_3 per 100 cc.
Solution 4— 9 mg. decrease As_2O_3 per 100 cc.
Solution 5—10 mg. decrease As_2O_3 per 100 cc.
Solution 9—11 mg. decrease As_2O_3 per 100 cc.
Solution 10—10 mg. decrease As_2O_3 per 100 cc.
Solution 11—12 mg. decrease As_2O_3 per 100 cc.
Solution 12— 9 mg. decrease As_2O_3 per 100 cc.

The average decrease in Group I was 6.25 mg., whereas in Group II it was 10.87 mg. The conclusion can be drawn here that the solutions of which Group I consists demonstrated the greatest stability over a period of sixty days. We find that potassium bicarbonate had been used in the preparation of three of the four solutions in this Group. The only other one containing potassium bicarbonate (No. 9) showed a total decrease of 11 mg., but inasmuch as the quantity used had been reduced to a greater extent in this solution, it would indicate that there must be a minimum amount of the salt required to furnish this stability. Solution No. 7, containing potassium carbonate and five per cent glycerin, also stood up very well.

CHART IV.



INGREDIENTS	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
$KHCO_3$			7.6			7.6		7.6	5			
KOH		5			5					3.4		
K_2CO_3				6			6				4	
ALCOHOL		50	50	50				30			50	50
GLYCERIN	100				50	50	50		50	50		

In the solutions in which potassium hydroxide had been used (2, 5, 10), there was an average decrease of 9.6 mg., showing it to be much less efficient than potassium bicarbonate. The other two solutions in which potassium carbonate was used (4, 11) showed an average loss of 10.5 mg. It is interesting to note that the stable solution using potassium carbonate contained glycerin, while the less stable ones were alcoholic. All solutions containing the lesser amounts of alkali or no alkali at all proved to be comparatively less stable.

Solution No. 12, which had been stored in a well-filled, glass-stoppered bottle, showed a total loss of only 9 mg. in 40 days, having exhibited no more decrease after 20 days. This mode of preservation apparently retarded its rate of decomposition, since it contained no alkali.

Very little can be said concerning the advantages of alcohol or glycerin over each other, except as previously mentioned in the case of the solutions made with potassium carbonate. The fact is, however, that none of the solutions showed any visible traces of moldy growths, indicating at this point, that either will function well as a preservative, providing 60 days is sufficient time for the development of a mold.

The commercial sample assayed 17 mg. of arsenic trioxide below the minimal amount allowed per hundred cubic centimeters by the U. S. P. It had a rather marked sedimentation, partly crystalline and partly gelatinous. As stated before, its age was indefinite, but its analysis gives us an idea of just how much deterioration can be ultimately expected using the U. S. P. formula. Only one of the solutions here prepared fell below the U. S. P. requirement, the latter being Solution No. 1 which contained no alkali at all.

Chart IV compares not only the decreases in strengths, but also the decrease rates. It will be noted that the rate is rather great at first, after which a point of equilibrium seems to be reached. The amount of air space in the bottle is probably a factor strongly influencing this initial drop. A further study of this Chart reveals the following points: Solutions Nos. 3, 8, 10, 12 all show no deterioration after 20 days; Nos. 9, 1 none after 30 days; Nos. 2, 4, 7 none after 40 days; and Nos. 5, 11 none after 50 days. No. 6 apparently has not yet reached a point of equilibrium.

CONCLUSIONS.

(1) Using equivalent quantities of potassium bicarbonate, potassium carbonate or potassium hydroxide in lesser amounts than indicated in the U. S. P., solutions may be prepared which do not fall below the official strength within a sixty-day period.

(2) The bicarbonate appears to be the most efficient of these three potassium salts in so far as stability of the product is concerned.

(3) The percentage of potassium bicarbonate may be advantageously reduced from the present 2 per cent to around 0.76 per cent, a decrease of over 60 per cent.

(4) In place of the 3 per cent of Compound Tincture of Lavender now used, about 5 per cent of alcohol or glycerin may be substituted, again providing no mold will appear after 60 days.

(5) Dispensers should be urged to make use of small bottles, well-filled and tightly stoppered, for storage purposes. This work is being continued.

ADDENDUM.

Fowler's Solution has been retained in the U. S. P. XI, but it is to be a colorless and flavorless solution. Apparently the Compound Tincture of Lavender was objectionable. That the alcohol present served a useful purpose has been suggested by various writers.

Mr. Schwartz was asked to conduct a series of time experiments, the results to date being herewith presented.

It is worth while noting that only one of the solutions has deteriorated below the U. S. P. minimum requirement. The suggestions offered in previous reports that the extractive in the Compound Tincture of Lavender stimulated oxidation of the trivalent arsenic may be substantiated by Mr. Schwartz's report if the solutions have reached a point of equilibrium, and will display no further deterioration. The selection of the alkali to be used and the quantity to be used will become a pharmaceutical problem. The problem of incompatibility will be a major one.—H. A. LANGENHAN.