

A STUDY OF THE STABILITY OF PHYSOSTIGMINE SOLUTIONS.*

BY JOHN C. KRANTZ, JR., AND FRANK J. SLAMA.¹

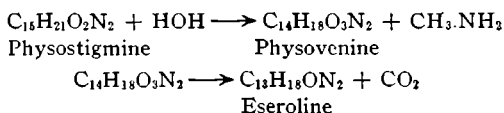
INTRODUCTION.

It is well known that solutions of the sulphate and salicylate of physostigmine become pink and even red after long standing and are unsuited for medicinal use. The rapidity of the change in color is dependent upon such factors as temperature, purity of the alkaloidal salt and the neutrality of the solvent. With the aim of preventing this color change two practical suggestions have been recorded in the literature²; one to dispense the salts in carbonated water and the other to employ a saturated solution of boric acid in water as a solvent when the solution is employed as a myotic. For more complete preservation than accomplished by the presence of carbonated water, the first author observed that the presence of an atmosphere of carbon dioxide—above the solution—preserved it in a colorless condition for a period of seven months and at the time of writing the solution is still colorless.

This investigation was begun in order to determine the nature of the action of these preservatives upon these alkaloidal salts.

THEORETICAL CONSIDERATION.

The reaction causing the decomposition of eserine is hydrolytic in nature and according to Salway³ takes place in the following manner:



Eseroline is the compound responsible for the formation of the red color. As carbon dioxide is one of the products of reaction, obviously the presence of this compound in the water would tend to prevent the hydrolysis of the alkaloid. Then, too, as the hydrolysis of the alkaloid is catalyzed by the presence of hydroxyl ions, carbon dioxide increases the hydrogen-ion concentration of the solution and also in this way retards hydrolysis. It is natural that a reagent which would tend to increase the hydrogen-ion concentration of the solution would retard the hydrolysis for it was observed that a solution of physostigmine sulphate 0.1% showed a p_{H} of 6.6 but after becoming pink the acidity increased to p_{H} 3.9.

When the solution of the alkaloidal salt is saturated with methyl amine the hydrolytic tendency is not checked although this is one of the products of decomposition as is carbon dioxide. The presence of methyl amine in the water greatly increases the hydroxyl-ion concentration and thus hydrolysis is immediately activated. Our experiments show that the decomposition is activated by the presence of oxygen and in an atmosphere of the pure gas the solution becomes pink within a period of a day. Thus it would seem that carbonated water above which there is an atmosphere of carbon dioxide should be the ideal preservative for these al-

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kaloidal salt solutions, as it tends to push back the hydrolytic action by increasing the concentration of one of the products of decomposition, by increasing the hydrogen-ion concentration and by preventing contact with atmospheric oxygen.

EXPERIMENTAL.

Samples of physostigmine sulphate and salicylate were prepared in concentrations of 0.1 per cent. Different solvents were employed and the length of time before the development of a pink color was observed.

The water employed for controls was double distilled and had a p_H of 5.8. The p_H of the other solvents was determined electrometrically with the exception of that of carbonic acid which was calculated from its degree of ionization in 0.1 molar solution.

The table shows the time in days required for the appearance of a pink color.

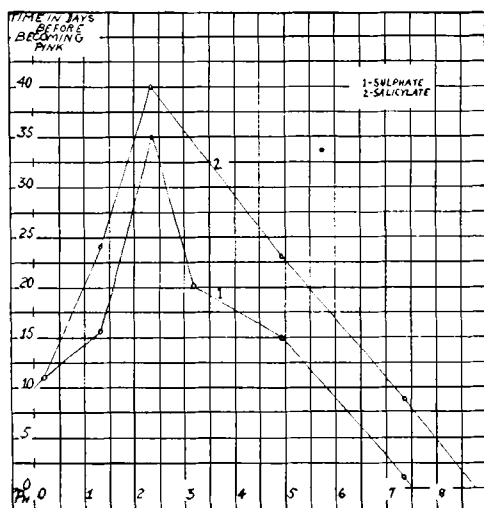
TIME IN DAYS REQUIRED FOR THE APPEARANCE OF PINK COLOR.

Eserine Sulphate in Water p_H 5.8 (Control)	Appearance of pink color on 5th day; 35th and 36th days, orange; 40th, red.
Eserine Salicylate in Water p_H 5.8 (Control)	Pink, 6th day; lavender, 19th to 22nd; light pink, 26th to 33rd; pink, 35th to 40th.
Eserine Salicylate in carbonated water p_H 3.77	Pink through to 40th from 21st day.
Eserine Sulphate in carbonated water p_H 3.77	Pink from 5th day to 36th; 40th, red.
Eserine Sulphate in carbonated water p_H 3.77 with an atmosphere of CO_2 above	Pink 33rd to 40th.
Eserine Sulphate in water p_H 5.8 with an atmosphere of CO_2 above	Pink 22nd to 40th.
Eserine Salicylate in salicylic acid p_H 2.45	None.
Eserine Salicylate in carbonated water p_H 3.77 with an atmosphere of CO_2 above	Pink 22nd to 40th.
Eserine Sulphate in HCl p_H 3.6	Pink 19th to 40th.
Eserine Salicylate in HCl p_H 3.6	Very slight pink 19th to 40th.
Eserine Sulphate in H_2SO_4 p_H 3.7	Pink 26th to 40th.
Eserine Salicylate in H_2SO_4 p_H 3.7	None.
Eserine Sulphate in H_3BO_3 p_H 3.7	Pink 26th to 40th.
Eserine Salicylate in H_3BO_3 p_H 3.7	Pink 26th to 40th.
Eserine Sulphate in water p_H 5.8 with an atmosphere of N_2 above	Pink 19th to 40th.
Eserine Salicylate in water p_H 5.8 with an atmosphere of N_2 above	Pink 19th to 40th.

The following graph on page 414 shows the effect of changes of hydrogen-ion concentration upon the sulphate and salicylate of the alkaloid. The hydrogen-ion concentration was increased in each case by the addition of hydrochloric acid to the solvent.

DISCUSSION OF RESULTS.

It will be observed from the table that under all circumstances the solutions of eserine salicylate were more stable than the solutions of the alkaloidal sulphate. A saturated solution of salicylic acid as a solvent renders the salicylate permanent over a long period of time and likewise sulphuric acid p_H 3.7 has a stabilizing influence in the salicylate solution. The presence of carbon dioxide in the water or atmosphere above the solution does not stabilize the solutions for a long period



Effect of changes of hydrogen-ion concentration upon the stability of eserine solutions.

of time. Carbon dioxide in water and an atmosphere of the gas above the solution gives a colorless solution for a long period of time, in some instances for five or six months in bottles which are almost completely filled. We attribute the preserving influence of carbon dioxide to its ability to increase the hydrogen-ion concentration of the solution, to push the hydrolytic reaction through mass action and also to prevent contact with atmospheric oxygen. The effect seems to be due to the combinations of influences of carbon dioxide as an atmosphere of nitrogen above the solutions did not serve to stabilize them nearly so well as one of carbon dioxide.

CONCLUSIONS.

1. Eserine sulphate and salicylate solutions can be kept colorless for a considerable period of time by adjusting the hydrogen-ion concentration of the solvent to a p_H between 2 and 3.
2. Carbonated water with an atmosphere of carbon dioxide above seems to be the best practical method of stabilizing these solutions.

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THE EFFECT OF GELATIN ON TITRATION CURVES OF VARIOUS ACIDS.*

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Incidental to the investigation of another problem it became necessary for the writer to construct titration curves for various acids in the presence of and in the absence of gelatin. The resulting curves show surprisingly little effect of gelatin on the titration curves of the various acids. Typical examples are given in Graphs Nos. 1, 2, 3 and 4.

It would seem in light of Loeb's theory of the amphoteric nature of gelatin that the two curves ought not, in each case, to be so nearly the same. Only very minor differences are apparent. Assuming the acid to be in chemical combination with the gelatin, ought we to expect the curves for the titration of the gelatin salt to sodium gelatinate to correspond so completely to that of the acid in each case?

* Scientific Section, A. Ph. A., Philadelphia meeting, 1926.

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