than on a weight calculated from the specific gravity. A variation of 0.1 cc. of tenth-normal sodium thiosulfate was the maximum noted in duplicate assays.

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## THE PRESERVATIVE CAPACITY OF SODIUM FORMALDEHYDE SULFOXYLATE IN CERTAIN MEDICINAL PREPARATIONS.*

BY JOHN C. KRANTZ, JR., C. JELLEFF CARR AND RUTH MUSSER.[1]

Recently sodium formaldehyde sulfoxylate has been employed in the treatment of bichloride of mercury poisoning in experimental animals and man by Rosenthal (1 and 2). This work has conferred therapeutic prominence upon this compound. In working with this substance in a study of its effect in rat sarcoma (3) the authors became interested in its properties as a reducing agent in the preservation of medicinal preparations. The stability of sodium formaldehyde sulfoxylate in acid and alkaline solutions has been studied by Jurist and Christiansen (4).

### MATERIALS AND METHODS.

The sodium formaldehyde sulfoxylate was obtained through the courtesy of Joseph Rosin, Merck and Co. Inc. of Rahway, N. J. The solutions studied under laboratory conditions in flint glass bottles were:

1. Epinephrine (in normal salt solution), 1–10,000
2. Physostigmine Salicylate, 0.2 per cent
3. Physostigmine Hydrochloride, 0.2 per cent
4. Morphine Sulfate, 1 per cent
5. Glycerite of Phenol
6. Solution of Resorcinol, 1 per cent
7. Sodium Bicarbonate-Sodium Salicylate, 6 per cent each.

To each of these solutions was added sodium formaldehyde sulfoxylate in concentrations of 1–500, 1–1000 and 1–5000, respectively. Observations for changes in color were made at 15-day intervals over a period of four months.

### RESULTS.

Over the four-month period all solutions containing sodium formaldehyde sulfoxylate as a preservative in each concentration employed prevented color change. On the other hand the control solutions in each instance showed signs of color change from within one to four weeks. The characteristic color changes produced by oxidation were not found in any of the preserved solutions.

### DISCUSSION.

The preservation of epinephrine solution has been the source of a considerable amount of investigation. Quite recently ascorbic acid has been employed for this purpose (5). In view of the fact that the pharmaceutical elegance of the preparation was preserved it was decided to test its medicinal potency. Under ether anesthesia, intravenous injections were made into dogs and the carotid blood pressure was measured. The results are shown in Table I. A study of

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TABLE I.

INFLUENCE OF EPINEPHRINE PRESERVED WITH SODIUM FORMALDEHYDE SULFOXYLATE UPON THE BLOOD PRESSURE OF A DOG.

8.6 Kg. Dog—Ether Anesthesia.

| Epinephrine, 1:33,000. | Blood Pressure Mm. Hg. Before. | After. | Change, Mm. |
|---|---|---|---|
| 1 cc. freshly prepared | 152 | 170 | +18 |
| 1 cc. from "Control Sample" | 156 | 160 | + 4 |
| 1 cc. with 1:500 S.F.S. | 155 | 155 | .. |
| 1 cc. with 1:1000 S.F.S. | 155 | 155 | .. |
| 1 cc. with 1:5000 S.F.S. | 154 | 154 | .. |
| 1 cc. with 0.6 mg. S.F.S. | 146 | 154 | + 8 |
| 1 cc. with 5 cc. 10 per cent S.F.S. | 144 | 156 | +12 |
| 1 cc. with 1 cc. 10 per cent S.F.S. 10 min. after mixing | 144 | 154 | +10 |
| 1 cc. freshly prepared | 148 | 164 | +16 |

Table I indicates that although sodium formaldehyde sulfoxylate protects epinephrine solutions against color change through oxidation, it simultaneously destroys its pressor response. The control solution, although red, retained some of its pharmacologic activity. The simultaneous injection of sodium formaldehyde sulfoxylate in 5 to 10 per cent solution with epinephrine did not obliterate the response of the latter. Mixing in the syringe prior to injection did not alter the epinephrine response. Apparently prolonged contact of the two compounds is necessary for sodium formaldehyde sulfoxylate to destroy the pharmacologic response of epinephrine.

With physostigmine solutions, myotic tests on the rabbit's pupil indicated full activity of the control solution which was definitely pink and those preserved with sodium formaldehyde sulfoxylate which remained devoid of color.

The sodium bicarbonate-sodium salicylate mixture is exceedingly interesting. As little as 1–5000 solution of sodium formaldehyde sulfoxylate preserves this well-known unstable mixture for at least four months. In the control solution definite darkening occurs within four days and within a month the bottle contains a black precipitate. As sodium formaldehyde sulfoxylate is a powerful reducing agent and exhibits a nearly neutral reaction, its preservative influence on this mixture of sodium bicarbonate and sodium salicylate again indicates that this change is an oxidative phenomenon as previously shown by two of the authors (6 and 7).

It is well known that sodium formaldehyde sulfoxylate solutions themselves undergo deterioration quite rapidly with the development of an alliaceous odor and a diminution of its reducing properties. Furthermore, the solution becomes quite acidic. The deterioration of a 1 per cent solution with respect to time was determined under laboratory conditions; one solution was preserved in distilled water, the other in a phosphate buffer $p_H$ 6.2. The diminution of the reducing properties was determined by titration with tenth-normal iodine. Chart I shows these effects.

CHART I.

An examination of Chart I indicates that the deterioration of the solution of sodium formaldehyde sulfoxylate is accompanied by the production of strongly

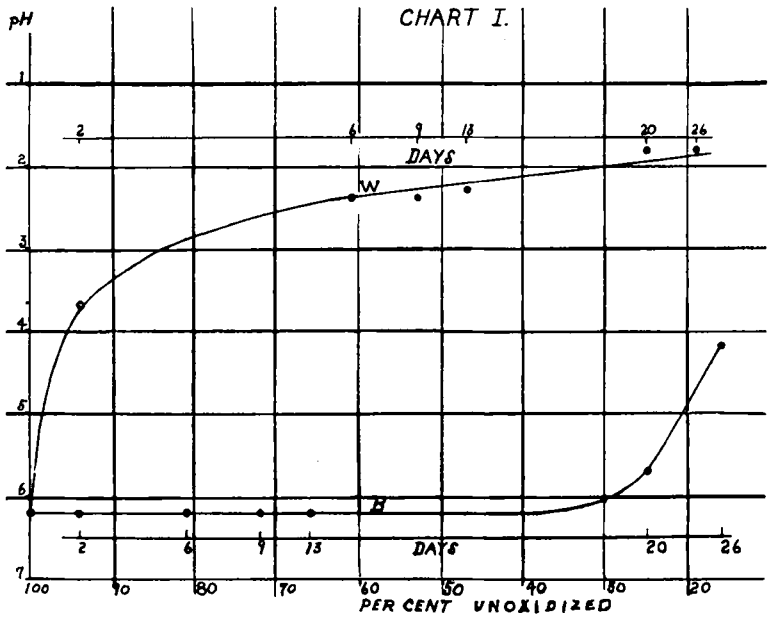
dissociated acid. If this acid is buffered the deterioration is retarded until the buffer capacity of the buffer salts is depleted, then the diminution in reducing power rapidly diminishes. It is possible that further studies along this line might be productive of a stable solution of this salt for intravenous medication.

## SUMMARY.

(1) Sodium formaldehyde sulfoxylate has been employed in certain medicinal preparations as a preservative. In concentrations of 1–5000, in which the alliaceous odor of its products of decomposition are not perceptible, the compound serves effectively as a preservative.

(2) The presence of sodium formaldehyde sulfoxylate in epinephrine solutions, upon standing, preserves the pharmaceutical elegance of the solutions but obliterates its pressor response.

(3) The buffering of solutions of sodium formaldehyde sulfoxylate to $p_H$ 6.2 with phosphates retards their rate of deterioration.

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