

SCIENTIFIC SECTION

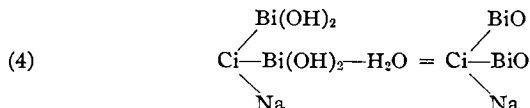
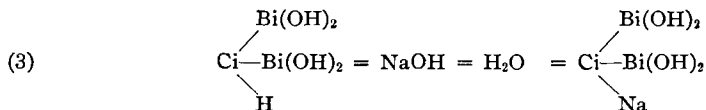
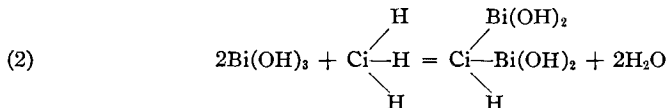
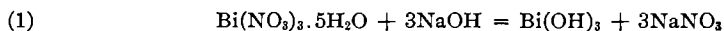
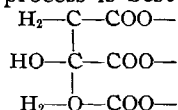
THE PREPARATION OF WATER-SOLUBLE SODIUM BISMUTH CITRATE.*

BY W. F. VON OETTINGEN.

In a previous paper (1) it was shown that a modification of the Fabrègue process yields mono bismuthyl citric acid, which under certain conditions forms with sodium hydroxide a dibismuthyl sodium citrate. The second part of this reaction is, however, rather complex, and it was shown that equimolecular quantities of dibismuthyl monosodium citrate and sodium citrate are formed. With this process the yield of a pure material is small, because the two compounds can only be separated by means of fractional precipitation with alcohol.

For this reason it seemed to be desirable to prepare a dibismuthyl citric acid and, by dissolving this in sodium hydroxide, the dibismuthyl mono sodium citrate. Telle (2) obtained a neutral bismuth citrate by boiling equimolecular parts of bismuth hydroxide and nitric acid in aqueous solution for five minutes. It appeared, therefore, feasible that, by changing the molecular quantities and the conditions, a dibismuthyl citric acid could be prepared. In order to obtain a pure preparation, it was necessary to start with a pure bismuth hydroxide which can be prepared by the method of Vanino and Zumbusch (3). The process is best

illustrated by the following equations, in which the citric acid radicle is represented by the abbreviation Ci:



Freshly prepared moist bismuth hydroxide is shaken with half the molecular equivalent of citric acid until the supernatant fluid is neutral or only slightly acid. Under these conditions, as will be shown below, dibismuthyl citric acid is formed, which is dissolved in sodium hydroxide with the formation of the dibismuthyl monosodium citrate, which is then precipitated by the addition of alcohol.

In detail the preparation is as follows:

(a) *Preparation of Bismuth Hydroxide.*—Ninety-seven grams corresponding to $\frac{2}{10}$ moles of bismuth nitrate are dissolved together with 40 Gm. of mannite in

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200 cc. of water and poured into an ice-cooled solution of 96 Gm. sodium hydroxide in 200 cc. of water of less than 5° C. If the two solutions are mixed slowly with continuous stirring, the temperature should not rise above 30° C., and the liquid should remain clear. After the mixture has been allowed again to cool below 5° C., ice-cold diluted 10 per cent sulphuric acid is added, until the mixture is nearly neutral (p_H 7.2). During this acidulation the bismuth hydroxide is precipitated. At the end of the reaction, it is filtered off, washed with water and several times resuspended in water, filtered and washed again until the diphenylamine test for nitric acid has become negative. The bismuth hydroxide represents a more or less colloidal substance, which after drying on clay plate forms a white amorphous powder, the purity of which may be illustrated by the following analysis:

Substance: 0.4976 Gm. = Bi_2S_3 0.4957 = 80.6 per cent Bi
 Substance: 0.5004 Gm. = Bi_2S_3 0.4970 = 80.4 per cent Bi
 Calculated for $Bi(OH)_3H$: 80.3 per cent Bi.

(b) *Preparation of Dibismuthyl Citric Acid.*—The undried bismuth hydroxide is transferred to a shaking container and half the equimolecular quantity (19 Gm.) of citric acid dissolved in 100 cc. of water is added. This mixture is kept for some days with occasional shaking on the shaking machine for some hours, until equilibrium has been established, *i. e.*, until all citric acid has been bound and the supernatant fluid is neutral, or only slightly acid to litmus paper. The dibismuthyl citric acid is then filtered off and washed carefully. The dried material represents a fine white powder.

Substance: 0.5016 Gm. = Bi_2S_3 0.4020 Gm. = 65.1 per cent Bi
 Substance: 0.4993 Gm. = Bi_2S_3 0.4000 Gm. = 65.1 per cent Bi
 Calculated for $Ci(BiO)_2$: 65.2 per cent Bi.

(c) *Preparation of Dibismuthyl Monosodium Citrate.*—The undried dibismuthyl citric acid is transferred into a beaker with 100–200 cc. of water and by constant stirring transformed into a homogeneous magma. A few cc. of phenol red solution (0.04%) are added and sodium hydroxide is then added from a burette, with constant stirring, until the material is dissolved. Usually a little more than one mole sodium hydroxide is required for this purpose. Sometimes a more or less marked turbidity persists, which is due to small quantities of bismuth hydroxide, which did not react during process *b*, or which were formed by the too rapid addition of the sodium hydroxide. In order to prevent the latter the p_H should be watched carefully, and the mixture should never become more alkaline than p_H 7.6. This turbidity is filtered off by passing the material several times through a layer of kaolin until it appears perfectly clear. From this solution the dibismuthyl sodium citrate is then precipitated by the addition of alcohol, filtered off, washed and dried. During the drying, the gelatinous precipitate assumes a glassy appearance and can be ground in a mortar to a white amorphous powder. This dried material has to be

$$\begin{array}{c} \text{Bio} \\ \diagdown \quad \diagup \\ \text{Ci} \text{---} \text{BiO} \\ \diagup \quad \diagdown \\ \text{Na} \end{array}$$

considered as the anhydride of the compound

$$\begin{array}{c} \text{Bi(OH)}_2 \\ \diagdown \quad \diagup \\ \text{Ci} \text{---} \text{Bi(OH)}_2 \\ \diagup \quad \diagdown \\ \text{Na} \end{array}$$

reason it is rather hygroscopic. The yield ranges from 70–80 per cent.

Substance: 0.4804 Gm. = Bi_2S_3 0.3726 = 62.9 per cent Bi

Substance: 0.4795 Gm. = Bi_2S_3 0.3702 = 62.7 per cent Bi

Calculated for $\text{Ci}(\text{BiO})_2\text{Na}$ = 63.0 per cent Bi

(d) *Precautions.*—Occasionally the bismuth content of the final product is too high, ranging from 63.9 to 66 per cent of bismuth, presumably due to adsorbed bismuth hydroxide. Such preparations can be purified by dissolving the material in water, filtering through kaolin and reprecipitating with alcohol.

Comparison of the physico-chemical properties of the dibismuthyl monosodium citrate obtained with the new and the old process.

Although the bismuth content of the dibismuthyl monosodium citrate, obtained with the method just described, was the same as that of the preparation obtained with the modified Fabrègue process, it seemed necessary to check the physico-chemical properties of the two compounds, in order to make sure that they are identical.

Effect of Heat.—2.5 per cent solutions of the two preparations containing 0.5 cc. of phenol red per 10 cc. as indicator were heated in sealed test-tubes to 50°, 100° and 150° C. for one-half, one and one and a half hours, and the changes of the p_{H} and changes of the solution were recorded.

TABLE I.—EFFECT OF HEAT ON 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE OBTAINED WITH THE NEW AND WITH THE OLD METHOD.

Temperature.	Time.	New Preparation.		Old Preparation.	
		p_{H} .	Precipitate.	p_{H} .	Precipitate.
50	30	7.4	No	7.6	No
	60	7.4	No	7.6	No
	90	7.4	No	7.6	No
100	30	7.4	No	7.3	Slight turb.
	60	7.4	No	7.3	Slight turb.
	90	7.4	No	7.3	Slight turb.
150	30	7.2	Mass. prec.	7.3	Mass. prec.

Table I shows that both solutions have practically the same stability toward heat, the slightly more alkaline preparation obtained with the older method being somewhat less resistant. When, however, both solutions are adjusted to the same p_{H} 7.4, this difference disappears, so that it may be stated that both preparations show the same resistance toward heat.

TABLE II.—EFFECT OF HYDROGEN-ION CONCENTRATION ON 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE OBTAINED WITH THE NEW AND THE OLD METHOD.

p_{H} .	New preparation.	Old preparation.
9.24	Mass. prec.	Mass. prec.
8.2	Distinct prec.	Distinct prec.
8.0	Distinct turb.	Distinct turb.
7.9	Slight turb.	Slight turb.
7.6	Clear	Clear
7.0	Clear	Clear
6.4	Clear	Clear
6.0	Clear	Clear
5.4	Clear	Clear
5.0	Turbid	Turbid

Table II shows that both preparations behave exactly alike toward change of the hydrogen-ion concentration, so that it appears that they are identical.

Effect of Changes of the Hydrogen-Ion Concentration.—In these experiments 10-cc. samples of the two solutions containing 0.5 cc. phenol red solution were adjusted to different p_H by the addition of small quantities of $N/10$ hydrochloric acid or $N/10$ sodium hydroxide.

SUMMARY.

A method is described, which allows the preparation of pure dibismuthyl monosodium citrate, with a good yield.

The preparation obtained with this method is identical with the compound obtained with the modified Fabrègue method.

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AMINOALCOHOLS VI—A STUDY OF THE ACTION OF PHENYLPROPANOLAMINE UPON THE BLOOD SUGAR OF RABBITS.*

BY JOHN C. KRANTZ, JR., AND WALTER H. HARTUNG.

INTRODUCTION.

It was established years ago by Blum (1) that injections of a solution of epinephrine caused hyperglycemia and often glycosuria. For some time it was considered that the elevation of the blood-sugar level was caused by increased glycogenolysis in the liver (2). Recent investigations by Cori (3) using more refined analytical methods indicate that the importance of the liver in the hyperglycemia is only secondary and further that the factor of primary importance in producing the accumulation of sugar in the blood is the decreased utilization of the sugar in the peripheral tissues.

Since the introduction of ephedrine into clinical medicine by the classical investigations of Chen and Schmidt (4), Wilson (5) at the suggestion of Chen studied the effect of this compound related to epinephrine upon the blood sugar of dogs and rabbits and observed a definite hyperglycemia. This action is claimed by Nagel (6) to be characteristic of the sympathomimetic amines.

Out of these Research Laboratories has come a series of synthetic arylalkanolamines (7) which because of their analogy to and homology with ephedrine were examined as to their effect on blood sugar in rabbits. Since phenylpropanolamine, a primary amine, has a pharmacological action much like that of ephedrine (Chen 8), a secondary amine, and because of its possible therapeutic interest, the effect of this compound was examined more extensively than the others.

METHOD OF STUDY.

Rabbits were starved twenty-four hours prior to the administration of the drug. The blood-sugar determinations were made by the method of Shaffer and Hart-

*Scientific Section, A. P. H. A., Baltimore meeting, 1930.