STUDIES ON THE PREPARATION AND TOXICITY OF MENTHYLSUCCINIC ACID AND ITS HEAVY METAL SALTS.*

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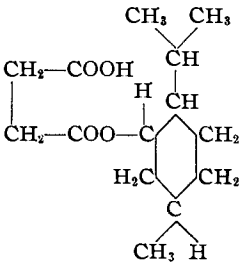
Mono-menthyl-succinic acid was first described by Zelikow (1) and Arth (2) and its silver salt prepared. It had been noted previously (3) that mono-esters of poly-carbonic acids frequently form heavy metal salts which have the faculty of being soluble in vegetable oils, such as olive, sesame, peanut and sweet almond. It was also noted that this oil solubility seemed to increase with the increase in the chain length of the alcohol which forms such a mono-ester. It was to be expected therefore that heavy metal salts of mono-menthylsuccinic acid might be soluble in vegetable oils.

PREPARATION OF MENTHYLSUCCINIC ACID.



900 Gm. succinic acid and 720 Gm. menthol were heated for three hours in an oil-bath at 175–180° C. After cooling, 1500 cc. 95% alcohol were added. This was filtered and washed with a little alcohol. 267.8 Gm. succinic acid were recovered. The alcoholic solution was poured into a solution of 434 Gm. $Na_2CO_3.H_2O$ in 15 liters of water. The insoluble material was filtered and washed with water. 205.5 Gm. remained which, after recrystallization from methanol, gave a melting point of 63.5° C. The melting point of di-menthyl-succinate is 64° C. Therefore, this substance, insoluble in Na_2CO_3 is di-menthyl-succinate.

The clear filtrate was slowly acidified with 393 Gm. H_2SO_4, dissolved in 2 liters of water. After cooling the precipitate was filtered off, washed with water and dried. The yield was 845.7 Gm., and the melting point was 54–56° C. Further purification was done by redissolving in a solution of 219.2 Gm. $Na_2CO_3.H_2O$ in 4000 cc. water and shaking out with ether. The water solution was then reprecipitated with dilute sulfuric acid. Yield: 699.3 Gm., melting point 62° C. The yields were as follows:

Succinic acid recovered	29.80%
Succinic acid in yield of menthyl-succinate	35.80%
Succinic acid in yield of di-menthyl-succinate	6.84%
Succinic acid accounted for	72.44%
Menthol in yield of menthyl-succinate	59.20%
Menthol in yield of di-menthyl-succinate	22.54%
Menthol accounted for	81.74%

Bismuth-tri-menthyl-succinate.

$$\begin{bmatrix} CH_2—CO_2C_{10}H_{19} \\ CH_2—CO_2— \end{bmatrix}_3 Bi$$

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769 Gm. menthylsuccinic acid (3 mols) were dissolved in 300 cc. warm ethanol and poured into a solution of 186 Gm. $Na_2CO_3.H_2O$ ($1^1/_2$ mols) in 400 cc. H_2O. To this solution was added, while stirring, at a temperature of 60° C., a solution of 481.5 Gm. Bi $(NO_3).5H_2O$ (1 mol) dissolved in 3000 cc. H_2O and 2400 cc. glycerine. The semi-solid precipitate was washed by decantation with water. The precipitate was taken up with 2000 cc. ether and the ether solution was washed several times with water and then dried with Na_2SO_4. After evaporation of the ether, a yield of 974.6 Gm. (85.5% yield) was obtained. The heavy yellow viscous material was assayed.

21.35% Bi found
21.45% Bi calculated.

This material was soluble in ethanol, menthanol, acetone, olive oil and oil of sweet almonds. It was insoluble in water.

TOXICITY TESTS FOR BISMUTH-TRI-MENTHYL-SUCCINATE (INTRAMUSCULARLY).

No. of Rats.	Mg. Metallic Bismuth per Kg. Body Weight.	Results.
6	250	4 died within 12–20 days 2 recovered
6	220	4 died within 13 days 2 recovered
6	175	All 6 remained alive

This shows that the toxicity was approximately 200 mg. Bi per Kg. body weight.

Basic Bismuth-Menthyl-Succinate.—When a sample of bismuth-tri-menthyl-succinate was treated with 85% methanol, a white solid material was formed which proved to be insoluble in absolute methanol. Its melting and decomposition point was 206° C. When dissolved in chloroform and poured into methanol, it could be reprecipitated. When over-heated, menthol odor could be detected. The analysis was 43.18% Bi.

Calculated for $\begin{matrix} CH_2—CO_2—C_{10}H_9 \\ | \\ CH_2—CO_2—Bi(OH)_2 \end{matrix}$ = 43.53% Bi

Manganese-Di-Menthyl-Succinate.—51.25 Gm. menthyl succinate (1/5 mol) dissolved in 500 cc. distilled water, containing 12.4 Gm. $Na_2CO_3.H_2O$ ($^1/_{10}$ mol). 44.5 Gm. manganese gluconate ($^1/_{10}$ mol) dissolved in 300 cc. water were added to the sodium-menthyl-succinate solution. A fine precipitate was formed which was taken up with ether. After washing, the ether solution was subjected to distillation. The residue (40.2 Gm.) was a pink powder and melted at 168–170° C.

Assay:

9.72% Mn found
9.71% Mn calculated for

$$\left(\begin{matrix} CH_2.CO_2.C_{10}H_9 \\ | \\ CH_2.CO_2— \end{matrix}\right)_2 Mn$$

The salt was insoluble in water, soluble in ether, chloroform and ethanol. Its solubility in cold olive oil and cotton seed oil was very low. However, 100 cc. of an olive oil solution containing 5% camphor dissolved 5.6 Gm. manganese-di-menthyl-succinate.

Silver-Menthyl-Succinate.—As stated previously, this product had been mentioned but not described in the literature. It was prepared as usual by reacting silver nitrate ($^1/_5$ mol) with sodium-menthyl-succinate ($^1/_5$ mol). A fine white powder was obtained. After drying for 1 hour at 100° C., the following silver assay was obtained.

29.65% Ag found
29.70% Ag calculated for

$AgCO_2—CH_2—CH_2—CO_2C_{10}H_{19}$

The melting point was 104° C. This salt appeared to be insoluble in vegetable oils and very little soluble in ethylene glycol and di-ethylene-glycol.

Attempts to prepare stable neutral lead and mercury salts of menthylsuccinic acid did not prove to be successful, if the above-mentioned method of preparation was employed. The lead salts obtained were basic salts and no definite salt could be isolated. The mercury compound obtained was found to be a menthylsuccinic acid mercuric chloride. When prepared from $^1/_6$ mol of sodium menthyl-succiniate solution and $^1/_{10}$ mol HgCl in aqueous solution, a yield of 41.1 Gm. of a white salt was obtained. After two recrystallizations from methanol a product with the following assay was obtained.

Found:

40.37% Hg
7.14% Cl

Calculated:

40.83%
7.22% for

$$\begin{array}{l} CH_2.CO_2C_{10}H_{19} \\ | \\ CH_2.CO_2.HgCl \end{array}$$

This salt was easily soluble in methanol, acetone and iso-propanol.

SUMMARY.

1. The bismuth, manganese, silver and mercury salts of menthylsuccinic acid were prepared and investigated for their faculty to dissolve in vegetable oils.

2. The bismuth and manganese salts were soluble, while the silver and mercury salts obtained were not.

3. The toxicity of the bismuth compound was approximately 200 mg. of metallic bismuth per Kg. body weight, when injected intramuscularly.

LITERATURE REFERENCES.

(1) Zelikow, *J. Russ. Phys.-Chem. Gesell.*, 34, 724; *Ber.*, 37, 1379 (1904).
(2) Arth, *Ann. chim. phys.* (6), 7, 433 (1886).
(3) Lauter and Braun, JOUR. A. PH. A., 25, 394 (1936).

THE SOLUBILITY OF LYOPHILE GELATINS.*

BY L. F. TICE.[1]

The ordinary commercial gelatins commonly employed are not, generally speaking, soluble to any appreciable extent in water at 25° C. When placed in water such gelatins absorb water to a considerable degree and become greatly swollen, but the individual particles originally present do not lose their identity nor have their number reduced. What has been interpreted as partial solubility by some workers is probably best explained as the exosmosis of lower molecular weight hydrolysis products from the swollen gelatin particle and their subsequent presence in the external aqueous medium. This seems borne out by the fact that gelatins of very low Bloom test, which are considerably hydrolyzed during manufacture, are actually found to slowly but completely dissolve in water at 25° C.

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