PREPARATION AND TOXICITY OF BISMUTH SALTS OF CAMPHORIC ACID ESTERS.*

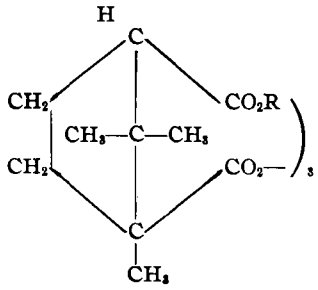
BY W. M. LAUTER AND H. A. BRAUN.[1]

The use of lipoid soluble bismuth preparations in the therapy of syphilis has increased interest in those salts of bismuth which are soluble in vegetable oils and are of low toxicity. It was in this connection that we began the investigation of three acid esters of camphoric acid and their bismuth salts.

The preparation of ortho-esters of *d*-camphoric acid has been described by Walker (1, 2), Ross and Sommerville (3), and by Edminson and Hilditch (4). We have followed Walker's (*loc. cit.*) method in preparing the ortho-methyl, ethyl and butyl esters of the acid.

Liebrecht (5) in a patent has given a general procedure for preparing bismuth salts of ortho- as well as allo-camphoric acid esters without furnishing proof of their constitution and purity. He does, however, make reference to their strongly trypanocidal action.

Walker (1, 2) and Edminson and Hilditch (4) prove that the reaction between camphoric anhydride and sodium alcoholates gives a quantitative yield of ortho-alkyl-hydrogen-camphorates, and that no allo-esters are formed. The reaction product, therefore, is in each case a neutral bismuth salt of the following constitution:



Bi where R represents an alkyl group.

Preparation of Bismuth-Tri-Methyl-Camphorate.—45.5 Gm. *d*-camphoric acid anhydride are slowly added to a solution of 5.75 Gm. sodium in 290 cc. methanol. After standing for 2 hours the solution is evaporated to a volume of 90 cc. The white crystals are filtered cold and washed with a few cc. of methanol. The yield is 33.4 Gm. sodium-methyl-camphorate or 59% of the calculated yield. The material left in the methanol solution was discarded.

33.4 Gm. sodium-ortho-methyl-camphorate were dissolved in a solution composed of 100 cc. H_2O and 75 cc. glycerine. 23 Gm. $Bi(NO_3).5H_2O$ were dissolved in an equal amount of the same aqueous glycerine solution. The bismuth nitrate solution was added slowly, while stirring, to the solution of the sodium salt. A white precipitate was formed. It was found that the elimination of the last traces of glycerine could only be accomplished by dissolving the product in ether, washing the ether solution with water and subsequent drying with Na_2SO_4.

A yield of 30.0 Gm. was obtained. The presence of some more bismuth-methyl-camphorate could be shown in the water-glycerine solution, but its recovery was not attempted. The yield is 83.6%. The melting point is 60.5–62.5° C.

The analysis is as follows: 0.3000 Gm. vacuum dried salt gave 0.904 Gm. Bi_2S_3 = 24.50% Bi: Calculated, 24.64% Bi.

---

* Scientific Section, A. PH. A.

[1] From the Research Laboratories of The Upjohn Company, Kalamazoo, Michigan.

The solubility in vegetable oils mentioned previously by Liebrecht (5) was investigated. Oil of sweet almonds was used because of its superiority to most vegetable oils in resisting oxidizing agents.

0.7624 Gm. bismuth-ortho-methyl-camphorate was warmed with 4 cc. of oil of sweet almonds U. S. P. X, cooled and filtered. 2 cc. were analyzed for bismuth. 0.0428 Gm. Bi_2S_3 = 17.4 mg. Bi in 1 cc. = 7.061 Gm. bismuth-methyl-camphorate dissolved in 100 cc. room temperature saturated solution.

It was of pharmaceutical interest to determine the influence of certain compounds of therapeutic importance upon the oil solubility of this bismuth salt. It was found that oil of sweet almonds containing 0.5% anhydrous chlorbutanol by weight contained 17.60 mg. Bi per cc., or 7.142 Gm. salt in 100-cc. solution. The increase is therefore slight.

A decided and fully anticipated increase in solubility, however, was noted when 10% camphor by weight was added to oil of sweet almonds.

2 cc. of a room temperature saturated solution analyzed as follows: 0.0610 Gm. Bi_2S_3 = 24.8 mg. Bi per cc. = 10.07 Gm. bismuth-methyl-camphorate in 100 cc. solution.

Preparation of Bismuth-Tri-(Ortho-Ethyl-Camphorate).—The ethyl ester was prepared in an analogous manner by reacting sodium-ortho-ethyl-camphorate in a 50% (by weight) glycerine solution with a 50% (by weight) aqueous glycerine solution of $Bi(NO_3)_3$.

The heavy metal salt obtained is washed with water, finally dissolved in chloroform, the chloroform solution washed several times with water and finally dried with $MgSO_4$. The solvent is driven off by heating *in vacuo* for 1½ hours at 115° C. in an oil-bath. The yield is 63.6%. The salt melts between 54° and 57° C. The analysis shows it to be a neutral salt:

Found: 23.51% Bi.

Calculated for Bi $(C_8H_4CO_2C_2H_5.CO_2)_3$: 23.47% Bi.

The salt is easily soluble in ether, acetone, chloroform, ethylene-dichloride and vegetable oils.

Solvent.	Milligrams Bi/Cc. Metallic in a Room Temperature Saturated Solution.	Gm. Bismuth-Ethyl-Camphorate in 100 Cc. Solution at Room Temperature.
(1) Oil of sweet almonds, U. S. P. X	39.5	16.03
(2) Oil of sweet almonds + 0.5% anhydrous chlorbutanol	41.82	16.97
(3) Oil of sweet almonds + 10% camphor	94.1	38.18

The influence of heat was studied by heating the salt for 16 hours at 160° C. It assumed a darker color. The product obtained was isolated by dissolving it in ethyl acetate and pouring the solution into methanol. A white salt was obtained insoluble in oil of sweet almonds and melting over a range of 204–220° C., while the bismuth-ethyl-camphorate had a melting point of 54–57° C. The analysis was as follows: 0.3000 Gm. gave 0.0954 Gm. Bi_2S_3 = 25.86% Bi.

It is probable that the ethyl groups have been split off because the camphoric acid molecule itself is quite stable, and without the presence of moisture there is no reason to assume the formation of a basic bismuth salt. The analysis also contradicts that. Furthermore a neutral bismuth-camphorate, prepared by reacting sodium-camphorate with $Bi(NO_3)_3$ gave a bismuth-camphorate insoluble in vegetable oils. When bismuth-ortho-ethyl-camphorate was heated at 250° C. in a 40-mm. vacuum, white crystals could be detected in the reception flask which, after

recrystallization from hot alcohol, were found to have a melting point of 220–221° C. and were identified as camphoric anhydride.

The solubility of this bismuth salt in oil of sweet almonds, U. S. P. X, was investigated and the data shown on preceding page were obtained.

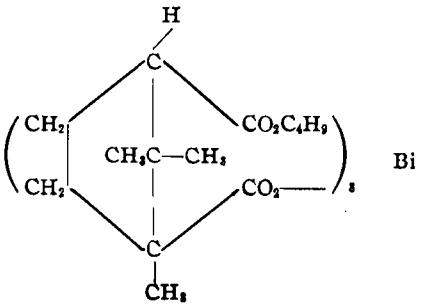
The addition of 10% camphor, as in the case of the methyl salt, increases the solubility to a considerable degree. The greater solubility of the ethyl compound compared with the methyl compound is apparent.

Preparation of Bismuth Tri-(Ortho-n-Butyl-Camphorate).—The sodium-ortho-*n*-butyl-hydrogen-camphorate is prepared according to Edminson and Hilditch (4) by reacting 1 mol. camphoric anhydride with 1 mol. sodium-*n*-butylate in a solution of *n*-butanol. After removing the excess butanol by evaporation *in vacuo* on a steam-bath the salt is obtained as a viscous oil, easily soluble in water.

40.5 Gm. $Bi(NO_3)_3.5H_2O$ are dissolved in a solution of 75 cc. glycerine in 100 cc. H_2O, and this salt solution is then added slowly, while stirring and cooling to a solution of 69.5 Gm. sodium-ortho-*n*-butyl-camphorate in 150 cc. H_2O + 90 cc. glycerine. The viscous heavy precipitate is washed several times with water, then dissolved in ether, and the ether solution is washed until no more glycerine could be detected in the washings. The ether is evaporated and the residual very viscous oil is then dried *in vacuo* at 115° C. for $^1/_2$ hour. The further purification is achieved by redissolving the salt in cold methanol and precipitating it again by pouring it into water. The clear yellow oil is then washed with water, taken up again in ether and the ether solution dried with Na_2SO_4. The bismuth salt is now dried *in vacuo* at 100–150° C. for $1^1/_2$ hours. The yield is 65.7 Gm. = 73.5% of the calculated amount.

The analysis is as follows:

20.95% Bi found
21.38% Bi calculated for:



Comparative Toxicity of the Camphorates.—In these experiments, it was our object to determine the minimum lethal dose (M. L. D.) which is the dose which will kill more than 50% of the animals. The M. L. D. of the three compounds was determined on white rats weighing between 150–250 Gm. The experimental procedure consisted of injecting the three compounds individually into the leg muscles of the rat. Since the toxicity of bismuth compounds is to a large extent determined by their metallic Bi content and their rate of absorption, both of these factors were taken into consideration in our studies. The doses injected were calculated on the basis of the metallic Bi content for each preparation which for the methyl was 17.6 mg. of metallic Bi/cc., for the ethyl was 40 mg. of metallic Bi/cc. and for the butyl 43.3 mg. of metallic Bi/cc. The animals were kept under observation for thirty days.

No manifestations of irritation at the point of injection were noted on gross observation after 24 hours, 3 days, 7 days, 14 days, 21 days or 30 days. We ob-

served no indications of pain or stiffening around the point of injection. All three preparations contained small amounts of chloretone which might account for freedom from pain for a short time after injection.

Toxic symptoms with larger doses did not appear until about the sixth or eighth day after injection and death usually occurred from the fourteenth to the twenty-first day. Typical symptoms of bismuth poisoning consisting of emaciation and loss of appetite were noted.

The results of these experiments included in Table I indicate that the M. L. D. for the bismuth-methyl-camphorate is 350 mg. metallic bismuth per Kg. of rat. The bismuth-ethyl-camphorate has an M. L. D. of 250 mg. Bi/Kg. while the bismuth-butyl-camphorate is the most toxic with an M. L. D. of 150 mg. Bi/Kg. of rat.

TABLE I.—TOXICITY OF BISMUTH-CAMPHORATES IN RATS.

Bismuth-Methyl-Camphorate.				Bismuth-Ethyl-Camphorate.				Bismuth-Butyl-Camphorate.			
Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Survival.	% Mortality.	Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Survival.	% Mortality.	Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Survival.	% Mortality.
100	5	..	0.0 %	75	5	..	0.0 %	100	5		0.0 %
150	10	24	20%	100	10	17	10%	150	10	18	60%
200	10	16	30%	125	5	30	20%	200	10	18	70%
250	10	18	20%	150	5	..	0.0%	300	5	17	80%
300	20	12	30%	200	10	15	30%				
350	10	12	80%	250	10	16	70%				
400	5	6	100%	300	10	15	80%				
				400	10	12	100%				

SUMMARY.

The preparation of the ortho-methyl, ethyl and *n*-butyl esters of the bismuth salt of camphoric acid has been described and their solubility in oil was investigated.

The toxicity in oil solutions was determined by intramuscular injections into albino rats.

REFERENCES.

(1) Walker, *J. Chem. Soc.*, 61, 1088 (1892).
(2) Walker, *Ibid.*, 63, 496 (1894).
(3) Ross and Sommerville, *Ibid.*, 2770 (1926).
(4) Edminson and Hilditch, *Transactions, J. Chem. Soc.*, 225 (1910).
(5) Liebrecht, German Patent No. 461,830 (1928).

PREPARATION OF BENZOYL PERSULPHIDE.*

BY E. MONESS, W. A. LOTT AND W. G. CHRISTIANSEN.[1]

Some preliminary clinical results obtained by Drs. Amberg and Brunsting of the Mayo Clinic had indicated that benzoyl persulphide might prove very useful in the treatment of certain selected types of dermatosis in which pruritis was the

* Scientific Section, A. PH. A., Portland meeting, 1936.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, N. Y.