REFERENCES.

(1) *Am. Jour. Pharm.*, 72 (1900), 342.
(2) *Lancet*, 1 (1902), 110; *Jour. Chem. Soc.*, 81 (1902), 874; *Chem. Abs.*, 9 (1915), 2403.
(3) *Arch. der Pharm.* (2), 85 (1856), 145.
(4) *Am. Jour. Pharm.*, 48 (1876), 353.
(5) *Gaz. chim.*, 10 (1881), 349; *Am. Jour. Pharm.*, 53 (1881), 56.
(6) *Ber.*, 23 (1890), 464; *Jour. Chem. Soc.*, 81 (1902), 874; *Chem. Abs.*, 4 (1910), 2864; *Ibid.*, 9 (1915), 2403; *Ibid.*, 16 (1922), 3109; *Ibid.*, 17 (1923), 3509.
(7) *Chem. Abs.*, 9 (1915), 623.
(8) "Brit. Yearbook," 1924, 19; *Chem. Abs.*, 20 (1926), 767.
(9) *Jour. Chem. Soc.*, 1906 Abs., 386.
(10) *Ibid.*, 94, ii (1908), 57; "Brit. Yearbook, 1907, 158; *Chem. Abs.*, 2 (1908), 300.

SEATTLE, WASH.,
October 1, 1932.

STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. V. BISMUTH COMPOUNDS OF CATECHOL, PYROGALLOL AND GALLIC ACID.*

BY W. M. LAUTER, A. E. JURIST AND W. G. CHRISTIANSEN.

The bismuth compounds of catechol, pyrogallol and gallic acid have received only a limited amount of study as anti-syphilitics. Substantially no information is available comparing them to other bismuth compounds to determine their relative toxicity and absorption. The preparation of bismuth subgallate was discussed by Schamelhout (1) and others, and other bismuth gallates by Bianquis (2) and by Sazerac and Levaditi (3), and the biological characteristics of these substances has been described by Didry (4) and by Sazerac and Levaditi (5). The preparation of bismuth compounds of catechol has been described by Weinland and Sperl (6) and by Rosenheim and Baruttschisky (7). The use of bismuth compounds of pyrogallol has been discussed by Sazerac and Levaditi (5) who studied their action as anti-syphilitics.

In this paper the preparation of several bismuth compounds of gallic acid is described and they are compared as regards their toxicity and absorption. Also the preparation of bismuth derivatives of catechol and pyrogallol is described. The latter, owing to their insolubility, were not studied to determine their toxicity and absorption because it was most unlikely that they would be readily absorbed.

TABLE I.

Compound Injected.	Medium for Injection.	Concentration Mg. Bi/Cc.	Approximate Maximum Tolerated Dose—Mg./Bi Kg. Body Weight.	Per cent Absorption.
Sodium bismuth digallate	Water	50	Less than 400	60
Sodium bismuth digallate	Olive oil	40	Less than 400	60
Sodium bismuth methyl gallate	Olive oil	50	Less than 400	60
Sodium bismuth gallate	Water	40	Less than 40	68*

* The rats injected died in less than 72 hours.

* Scientific Section, A. PH. A., Toronto meeting, 1932.

The compounds tested were studied to determine their toxicity and absorption in the same manner as was previously employed in studying the other bismuth compounds discussed in previous publications. The compounds were injected intramuscularly into albino rats in aqueous solution or oil suspension. The absorption was determined by quantitative estimation of the unabsorbed bismuth remaining at the site of injection. The toxicity was estimated from the growth curves of the injected animals. The results obtained are given in the foregoing table.

The results show that sodium bismuth digallate is much less toxic than sodium bismuth gallate but that the absorption is not entirely satisfactory compared to the tartrates and mucates which are much more readily and completely absorbed (cf. paper II of this series). There is apparently little difference in the absorption and toxicity of sodium bismuth digallate and sodium bismuth methyl gallate whether in aqueous solution or olive oil suspension. However, these compounds are not very stable in aqueous solution since these solutions darken quite rapidly on standing. From the clinical standpoint, while sodium bismuth digallate and sodium bismuth methyl gallate are relatively low in toxicity, their slow and incomplete absorption renders them of doubtful value. Sodium bismuth gallate is not very much better absorbed but is far more toxic.

If the results described in this and previous publications are reviewed, it becomes apparent that the bismuth salts of fatty acids are relatively of the same order of toxicity as the tartrates and mucates, excepting sodium potassium bismuth tartrate which is much more toxic than the others. However, they are not nearly as completely absorbed. The iodobismuthates of the alkaloids are more toxic that the fatty acid salts, tartrates and mucates, with the sole exception of the iodobismuthate of procaine which is of the same order of toxicity as the bismuth tartrates. They are also incompletely absorbed. The bismuth compounds of thioglycollic acid are not completely absorbed, and are much more toxic than the bismuth mucates, the bismuth tartrates, the bismuth salts of the fatty acids and the bismuth compounds of gallic acid, excepting sodium bismuth gallate which is of the same order of toxicity as the thioglycollates. Sodium bismuth digallate and sodium bismuth methyl gallate are of the same order of toxicity as the tartrates but are not nearly as well absorbed. Consequently it appears that from the standpoint of toxicity and absorption, sodium or potassium tribismuth tartrate is the most satisfactory therapeutic agent of this series of compounds. However, it has been pointed out elsewhere (8) that these latter compounds are very irritating on intramuscular injection, causing severe local reactions. Therefore, it must be concluded that none of the compounds so far described in this series of studies are entirely satisfactory bismuth anti-syphilitic agents although many of them have already been used extensively in the treatment of syphilis.

EXPERIMENTAL PART.

Preparation of Sodium Bismuth Gallate.—Eleven Gm. of gallic acid were dissolved in 300 cc. of hot water and a solution of 17.6 Gm. of sodium bismuth tartrate in 300 cc. of water were added. A fine yellow precipitate was obtained which was collected on a Buchner funnel and washed with water, alcohol and

ether. When dry, the salt contained 51.52% of bismuth. Ten Gm. of this solid were then dissolved in dilute sodium carbonate solution and an equal volume of alcohol was added. A brown oil formed which became solid when treated several times with absolute alcohol. Finally, it was washed with ether. The solid contained 42.66% of bismuth and was readily water soluble, giving a dark brown solution.

The formula of this compound is $C_7H_4O_6BiNa_3$, having a theoretical bismuth content of 50.24%, showing that there was in it some bismuth digallate.

Preparation of Sodium Bismuth Digallate.—Ten Gm. of the above preparation were dissolved in 100 cc. of water and 50 cc. of bismuth subnitrate solution, prepared by diluting a solution of 150 Gm. of bismuth subnitrate in 150 cc. of concentrated nitric acid (sp. gr. 1.41) to one liter, were added. A yellow precipitate formed which was collected on a Buchner funnel, washed with water, alcohol and ether. The dry solid contained 59.7% bismuth. Ten Gm. of this were then dissolved in a dilute aqueous solution of sodium gallate. A dark oil was precipitated by the addition of acetone. The supernatant liquid was decanted and the oil was washed twice with acetone, three times with absolute alcohol which converted it into a solid, and then twice with water. The dry solid contained 32.6% of bismuth and was readily water soluble.

The formula of sodium bismuth digallate is $C_{14}H_9O_{11}BiNa_2$, having a calculated bismuth content of 28.13%. This compound was apparently a mixture containing some sodium bismuth gallate.

Preparation of Sodium Bismuth Methyl Gallate.—Ten Gm. of methyl gallate were dissolved in 150 cc. of warm water. 104 cc. of the same bismuth nitrate solution as was used above were added, and a yellow precipitate formed. This was collected on a Buchner funnel and washed with water, alcohol and ether. The water-insoluble substance contained 49.56% of bismuth. Ten Gm. of this solid were then suspended in water and a slight excess of dilute aqueous sodium hydroxide was added forming a dark red solution. Then 250 cc. of 95% alcohol were added, throwing down a fine yellow precipitate. This was collected on a Buchner funnel and washed with alcohol and ether. The readily water-soluble solid contained 49.03% of bismuth.

This substance has the formula $C_8H_9O_6BiNa_3$, containing 48.27% of bismuth.

Preparation of Bismuth Pyrogallate.—Twelve and six-tenths Gm. of pyrogallol were dissolved in 100 cc. of water and 346 cc. of a bismuth nitrate-mannite solution were added. The bismuth nitrate solution contained 48.5 Gm. of bismuth nitrate pentahydrate and an equal amount of mannite. The entire operation was carried out in an atmosphere of carbon dioxide to prevent oxidation. The yellow precipitate obtained was collected on a Buchner funnel and washed with water, alcohol and ether. The yellow solid was soluble in aqueous sodium hydroxide but was insoluble in water or sodium carbonate solution.

Calculated for $C_6H_3(OH)O_2BiOH$: Bi—59.7%; Found: Bi—59.24%.

Preparation of Bismuth Catecholate.—Thirteen Gm. of bismuth oxychloride were dissolved in 9 cc. of concentrated hydrochloric acid, and 30 cc. of saturated sodium chloride solution were added. Then saturated sodium carbonate solution

was added until a faint white precipitate was formed. The solution was then clarified and warmed, and mixed with a warm solution of 5.5 Gm. of catechol in 28 cc. of saturated sodium chloride solution. Then saturated sodium carbonate was added to the yellow solution until no further precipitate was obtained. The yellow precipitate was collected on a Buchner funnel, washed with water, alcohol and ether. The yellow solid was insoluble in aqueous sodium hydroxide but was soluble in hydrochloric acid.

The biological tests on these compounds were carried out in the Biological Laboratories of E. R. Squibb and Sons, New Brunswick, N. J.

(1) Schamelhout, *J. pharm. Belg.*, 8 (1926), 371.
(2) Bianquis, "Paris Thesis" (1922).
(3) Sazerac and Levaditi, *Ann. Inst. Pasteur*, 36 (1922), 1.
(4) Didry, "Paris Thesis" (1922).
(5) Sazerac and Levaditi, *Compt. rend. soc. biol.*, 86 (1922), 1064.
(6) Weinland and Sperl, *Z. anorg. allgem. Chem.*, 150 (1925), 69.
(7) Rosenheim and Baruttschisky, *Ber.*, 58B (1925), 891.
(8) Jurist and Christiansen, JOUR. A. PH. A., 20 (1931), 349.

RESEARCH DEPT. OF THE CHEMICAL & PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB & SONS, BROOKLYN, N. Y.

A STUDY OF SOME INCOMPATIBILITIES OF QUININE SULPHATE.

BY ALFRED BARTHEN, HERMAN EISENBERG AND FRANK A. LEE.

This paper is the result of a study of the incompatibilities that take place when quinine sulphate in aqueous solution is treated with any one of the following substances: Hypophosphorous acid, citric acid, acetic acid and an excess of the corresponding potassium salt is added to the mixture; also the incompatibility that results when quinine sulphate solution is treated with a solution of sodium salicylate. It has been stated that the corresponding quinine salt of the acid radical used is the substance precipitated, but in view of the fact that the acid mixture itself does not precipitate, and only after the corresponding potassium salt of the acid radical in question has been added that the actual precipitation is noticed, there is the possibility of the formation of a complex compound in each case, rather than the normal quinine salt. It was to investigate this possibility that the work was started.

EXPERIMENTAL PART.

QUININE ACETATE (1, 2).

Ten grams of quinine sulphate was added to 20 cc. of distilled water and 11 cc. of glacial acetic acid, producing a clear solution. To this solution was added 15.5 cc. of a solution of potassium acetate containing 12 Gm. of the salt. A voluminous precipitate formed immediately. The mixture was allowed to stand several hours to insure complete precipitation. The resulting precipitate was placed on a filter and washed until free from sulphates. It was dried on a porous plate and kept in a desiccator over sulphuric acid.