The assistance of Henry W. George in the preparation of the alkyl gallates is gratefully acknowledged.

The expenses necessary for the pursuance of this investigation have been met in part from a fund for research in the Department of Tropical Medicine, given by a citizen of Boston.

Summary

The following derivatives of gallic acid and pyrogallol are described: *iso*propyl gallate; *n*-butyl gallate; 2,3-dihydroxy-5-carboxyphenoxyacetic acid; methyl 2,3-dihydroxy-5-carbomethoxyphenoxyacetate; 3,4,5-trihydroxybenzoyl-glycolic acid; 3,4,5-trihydroxybenzoyl-glycolamide; 3-benzoyl-gallic acid; 3,5-dibenzoyl-gallic acid; 2,3-dihydroxyphenoxyacetic acid; methyl 2,3-dihydroxyphenoxyacetate; 2,3,4-trihydroxybenzylidine-2′-methyl-5′-sulfo-aniline; 2,3,4-trihydroxybenzylidine-sulfanilic acid; 2,3,4-trihydroxybenzylidine-anthranilic acid; N,N′-di-2,3,4-trihydroxybenzylidine-3,3′-diamino-4,4′-dihydroxy-arsenobenzene.

BOSTON 17, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

THE REACTION OF SOME POLYHYDRIC PHENOLS WITH SODIUM ANTIMONYL TARTRATE

BY WALTER G. CHRISTIANSEN

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Although antimony derivatives of polyhydric phenols are fairly well known, they have been ignored almost completely in chemotherapeutic investigations. In a brief discussion of antimonials derived from hydroxy compounds, Thomson and Cushny[1] dismiss them with a few words. While the studies reported herein were in progress, indications have appeared that the chemotherapeutic properties of antimony derivatives of compounds of the catechol series are being examined elsewhere;[2] in this Laboratory, attention has been concentrated on trihydroxybenzene derivatives.

Gallic acid and pyrogallol both react with alkali antimonyl tartrates in aqueous solution to give antimony derivatives of these phenols,[3] and they also afford excellent opportunities for the preparation of other polyhydric phenols by the introduction of different organic groups. Evidently, therefore, a means is at hand whereby the relation between the structure of the phenol and its reactivity with respect to an alkali antimonyl tartrate

[1] Thomson and Cushny, *Proc. Roy. Soc.* (*London*) **82B**, 252 (1910).

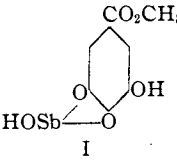
[2] (a) U. S. pat. 1,549,154 (1925); Brit. pat. 213,285 (1923). (b) Uhlenhuth, Kuhn and Schmidt, *Deut. med. Wochschr.*, **50**, 1288 (1924); *Arch. Schiffs-Tropen-Hyg.*, **29**, 623 (1925).

[3] (a) Rosing, *Compt. rend.*, **46**, 1140 (1858). (b) Causse, *Ann. chim. phys.*, (7) **14**, 551, 560 (1898).

as well as the chemotherapeutic properties of a series of closely related antimonials may be studied. The amide and the esters of gallic acid yield antimony derivatives just as readily as the free acid does. The nature of the alkyl group present in the ester is of little consequence; both simple alkyl groups and those containing substituents were used. When, however, the hydrogen atom of one of the hydroxyl groups in either pyrogallol or gallic acid is replaced by an organic residue, the phenolic compound will no longer react with sodium antimonyl tartrate to give an antimony derivative.[4] The hydroxy substitution products which were studied did not have the substituent attached to the central hydroxyl group of the pyrogallol or gallic acid molecule; they still contained two adjacent hydroxyl groups and were, therefore, catechol derivatives. 2,3,4-Trihydroxybenzaldehyde and its phenylhydrazone react with sodium antimonyl tartrate, but benzylidene derivatives obtained by treating sulfo-anilines with this aldehyde do not.

Those derivatives of gallic acid and pyrogallol which do not react with sodium antimonyl tartrate do react very slowly with antimony oxide when a suspension of the latter in an aqueous solution of the phenolic compound is refluxed.

The composition of the antimonial that precipitates when the phenolic compound reacts with sodium antimonyl tartrate in aqueous solution depends upon the experimental conditions existing at the time of reaction.[5] The products reported herein have approximately the composition required for formulas like I, but the variation from the theoretical is too great in most cases to permit the statement that pure substances of type I are obtained by this reaction. Thus, methyl antimony gallate (I) contains 37.94% of antimony as against a calculated value of 37.96, when it is prepared from methyl gallate and antimony trichloride according to the method of Causse[6] whereas the product obtained from methyl gallate and sodium antimony tartrate contains only 36.6% of antimony.



I

In all calculations the atomic weight of antimony is taken as 121.8.[7] These antimonials are all trypanocidally active; the results of the pharmacological studies will be published elsewhere.

[4] (a) A very small yield of an antimony derivative is obtained from 2,3-dihydroxy-5-carboxyphenoxyacetic acid. (b) This result is in agreement with the observation that catechol and sodium antimonyl tartrate do not react in aqueous solution. The absence of a white precipitate when aqueous solutions of catechol and sodium antimonyl tartrate are mixed is indicative of the failure of the compounds to react, because antimonyl catechol is insoluble in water.

[5] Sanin [*Z. Farben-Ind.*, 9, 2 (1910)] obtained three antimonyl tannic acids by varying the conditions under which the tannic acid was treated with tartar emetic.

[6] Ref. 3 b, p. 557.

[7] Willard and McAlpine, THIS JOURNAL, **43**, 797 (1921). Weatherill, *ibid.*, **46**, 2437 (1924). Hönigschmid, Zintl and Linhard, *Z. anorg. allgem. Chem.*, **136**, 257 (1924).

Experimental Part

The experimental procedure will be described in detail in only one case, and the results obtained by treating the various phenols with sodium antimonyl tartrate will be recorded in Table I. A few observations will be inserted to indicate the relation between the experimental conditions and the antimony content of the reaction product.

A boiling solution of 11 g. of gallic acid in 300 cc. of water is added to a boiling solution of 21 g. of sodium antimonyl tartrate (1.2 molecular equivalents) in 500 cc. of water; after a short time a dense, white precipitate

TABLE I

REACTION OF POLYHYDRIC PHENOLS WITH SODIUM ANTIMONYL TARTRATE

Phenolic compound used	Yield per 10 g. of poly-phenol G.	Sb found, %	Sb, calcd. for Ar  SbOH, %
Pyrogallol	8.4	45.6	$C_6H_5O_4Sb$: 46.3
2,3-Dihydroxyphenoxyacetic acid	0		
Methyl 2,3-dihydroxyphenoxy-acetate	0		
Gallic acid	12.3	38.5; 38.7	$C_7H_6O_6Sb$: 39.7
Methyl gallate	8.1	36.6	$C_8H_7O_6Sb$: 37.96
*iso*Propyl gallate	10.0	33.0	$C_{10}H_{11}O_6Sb$: 34.9
n-Butyl gallate	11.0	33.4	$C_{11}H_{13}O_6Sb$: 33.6
Gallamide[a]	3.0	40.0; 39.8	$C_7H_6O_5NSb$: 39.8
3-Benzoylgallic acid	0		
3,4,5-Trihydroxybenzoyl-glycolamide	11	30.9; 31.0 N: 3.80; 3.94; 3.72[b]	$C_9H_8O_7NSb$: 33.5 N: 3.85
3,4,5-Trihydroxybenzoyl-glycolic acid	6.5	36.7	$C_9H_7O_8Sb$: 33.4
2,3-Dihydroxy-5-carboxyphenoxy-acetic acid[c]	1.2	30.3; 30.5	$C_9H_7O_8Sb$: 33.4
Methyl 2,3-dihydroxy-5-carbo-methoxyphenoxyacetate	0		
2,3,4-Trihydroxybenzaldehyde	7.5	42.8	$C_7H_5O_5Sb$: 41.9
2,3,4-Trihydroxybenzaldehyde-phenylhydrazone[d]	7.7	24.6	$C_{13}H_{11}O_4N_2Sb$: 32.0
2,3,4-Trihydroxybenzylidene-2'-methyl-5'-sulfo-aniline	0		
2,3,4-Trihydroxybenzylidene-sulfanilic acid	0		

[a] The crude reaction product is extracted by boiling with 600 cc. of water, washing the insoluble residue with 200 cc. of water, re-extracting with 500 cc. of boiling water and washing with two 100 cc. portions of hot water. From the extracts, 35% of the gallamide originally used is recovered.

[b] This determination was made by dissolving the antimonial in concentrated sodium hydroxide solution and distilling into standard hydrochloric acid.

[c] The crude product is boiled twice with 25 cc. portions of water and the residue is washed with 30 cc. of hot water; 63% of the original polyphenol is recovered.

[d] The crude product is extracted at room temperature with alcohol.

forms. The reaction mixture is cooled and the reaction product is collected on a filter and washed with 100 cc. of water. In this case and some others, the crude material is suspended in 100 cc. of boiling water, cooled, re-collected and dried in a *vacuum* over sodium hydroxide; the yield is 13.6 g. and the product contains 38.6% of antimony.

If equivalent quantities of the reactants are used in solutions which are twice as concentrated as those described above and the gallic acid solution is heated only enough to prevent crystallization and the tartrate solution is kept at room temperature, the reaction product separates instantly and contains only 34.5% of antimony. After this material has been extracted with boiling water, it contains 35.2% of antimony.

When methyl gallate is treated with sodium antimonyl tartrate in aqueous solution in the manner described for the gallic acid derivative, precipitation begins several minutes after the hot solutions have been mixed; the yield is 6.6 g. from 8.2 g. of ester, and the antimony content of the product is 36.6%. If the reaction mixture is refluxed for two hours, the material which is obtained by filtering the hot mixture contains 36.1% of antimony, and the white precipitate which separates when the hot filtrate is cooled in the ice box contains only 33.4% of antimony. When 2 g. of methyl gallate is used, each of the two portions of reaction product weighs 0.7 g.

When aqueous solutions of the monosodium salts of the hydroxybenzylidene-sulfo-anilines are refluxed with antimony trioxide, the latter dissolves to some extent; definite products were not obtained.

Di-antimonyl Derivative of Di-2,3,4-trihydroxybenzylidene-3,3′-diamino-4,4′-dihydroxyarsenobenzene.—A warm solution of 1.8 g. of the antimonyl derivative of 2,3,4-trihydroxybenzaldehyde in 40 cc. of water and 10 cc. of hydrochloric acid is added to a warm solution of 1.47 g. of arsphenamine in 50 cc. of water. The yellow color immediately changes to orange and then an orange precipitate forms. After half an hour, the latter is collected by centrifuging and washed with water, hydrochloric acid (1:1) and two portions of water; the product is dried in a *vacuum* over sodium hydroxide. The orange-red powder (3 g.) is added to 200 cc. of water and 15 cc. of 10 *N* aqueous sodium hydroxide during mechanical stirring. As soon as the material has dissolved completely (about 90 seconds), 16 cc. of hydrochloric acid is added and the curdy brown precipitate is collected by centrifuging, washed twice with water and dried in a *vacuum* over sodium hydroxide. The dried product (2.1 g.) is deep orange.

Anal. Calcd. for $C_{26}H_{18}O_{10}N_2As_2Sb_2$: N, 3.07. Found: 3.19, 3.07.

The expenses necessary for the pursuance of this investigation have been met in part from a fund for research in the Department of Tropical Medicine, donated by a citizen of Boston.

Summary

1. The relation between the structure of certain polyhydric phenols and their reactivity with respect to sodium antimonyl tartrate has been studied.

2. The introduction of substituted and unsubstituted alkyl groups into the carboxyl group of gallic acid has little influence on this reaction.

3. The replacement of one of the hydroxyl hydrogen atoms of pyrogallol or gallic acid by an organic group prevents the reaction from taking place.

4. Certain benzylidene derivatives of 2,3,4-trihydroxybenzaldehyde do not react with sodium antimonyl tartrate.

5. The composition of the products depends upon the experimental conditions which are used.

6. Arsphenamine condenses readily with the antimonyl derivative of 2,3,4-trihydroxybenzaldehyde.

7. These antimonials are trypanocidally active.

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THE SEED AND OIL OF JOHANNESIA PRINCEPS

BY GASTAO ETZEL[1] AND C. G. KING

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Johannesia Princeps is a Brazilian tree belonging to the family Euphorbiaceae. It grows rapidly and equally well in a great variety of soils and produces an abundance of nuts which are used in Brazil for medicinal purposes. The kernels are almond-like in consistency, 10 to 20 g. each in weight, and have an agreeable flavor. By cold pressing, or extracting them with ether, a clear, slightly yellowish-green oil is obtained. The nuts and oil have been widely used for their laxative effect, and the latter has been used as a drying oil. Highly satisfactory results have been reported upon the use of the oil as a cathartic, by several authors,[2] who state that its particular advantages are agreeable flavor and odor, low viscosity, no intestinal irritation, no nausea and a potency about four times that of castor oil.

B. Niederstadt and Th. Peckol[3] made partial analyses of the oil, and M. Oliveira[2] reported the presence of an active principle (johannisin), analogous to ricinin, in the embryo of the seed.

[1] This paper is based upon a thesis submitted to the Graduate School of the University of Pittsburgh by Gastao Etzel in partial fulfilment of the requirements for the degree of Master of Science.

[2] Anon., *New Remedies*, **10**, 260–1 (1881); *Pharm. J. Trans.*, **41**, 380 (1881–1882); *Monit. Pharm.*, **1881**, 156.

[3] Niederstadt and Peckol, *Ber. Pharm. Ges.*, **15**, 225 (1905).