[Contribution from the Chemistry Department of the University of Kansas City and the Jensen-Salsbery Laboratories]

## Antimonial and Thioantimonial Derivatives of Catechol

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The chemotherapeutic agents employed to date in the treatment of heartworms in dogs have been substances developed for use in the treatment of human diseases, particularly schistasomiasis. Although many widely different types of compounds have been used the organic antimony compounds have given the best results. Colloidal antimony and antimony oxide preparations have been useless. Antimonyl tartrate and similar forms of solubilized antimony oxide have given some encouraging results, but the antimonial catechols and particularly fuadin<sup>1</sup> have given the best results. In an effort to obtain a more efficient agent we have studied two types of derivatives of antimonial catechol: (1) unsymmetrical derivatives of antimonial catechol containing an unsubstituted antimonial catechol molecule made soluble by a solubilizing group in a second molecule which is linked to the antimony atom of the antimonial catechol through the free hydroxy group; (2) thioantimonial catechols in which one or more of the oxygen atoms of antimonial catechol have been replaced by sulfur atoms.

One of these compounds, the sodium salt of antimonial catechol thiosalicylic acid, has been found to be a useful agent for the treatment of heartworms in dogs.<sup>2</sup> We have found this compound superior to those in which solubilizing groups are present in the catechol nucleus.

Both mono- and dithiocatechol form antimony derivatives. The mercapto groups of these compounds are more reactive than the hydroxyl groups of catechol.

## **Experimental Part**

Antimonial Catechol.—Preparation by a modification of the method of Causse.<sup>3</sup> Catechol (27.5 g., 0.25 mole) was dissolved in saturated sodium chloride solution (125 cc). Antimony trichloride (54.7 g., 0.24 mole) was dissolved in saturated sodium chloride solution (40 cc.). Keeping an excess of solid sodium chloride present the latter solution was neutralized with 2 N sodium carbonate solution until the precipitated antimony hydroxide just failed to redissolve. The resultant solution of antimony chloride was added slowly with stirring to the catechol solution. After stirring for one-half hour the precipitate formed was collected. Additional precipitate was obtained by diluting the filtrate to one liter. The combined precipitates were resuspended in one liter of water, stirred mechanically fifteen minutes and collected. This washing was repeated twice; 70% yield (based on antimony trichloride). Found: 49.6% Sb<sup>4</sup> (calcd. for antimonial catechol, o-C<sub>6</sub>H<sub>4</sub>O<sub>2</sub>SbOH, Sb = 49.4%). White microplatelets, insoluble in water, which do not melt or decompose below 300°.

Preparation by the use of antimony trifluoride. Antimony trifluoride (89.4 g., 0.5 mole) dissolved in 200 cc. of water was added with stirring to a solution of catechol (55 g., 0.5 mole) in an equal volume of water. Precipitation occurred at once. The mixture was stirred for one-half hour, filtered and washed three times by resuspension in 200-cc. portions of water with stirring; 55% yield. Found: 48.9% Sb, 7.4% F.<sup>§</sup> (Calcd. for fluoro antimonial catechol,  $o-C_6H_4O_2SbF$ : Sb, 49.0; F, 7.6%.) Boiled with 2 N sodium carbonate solution the fluoride was quantitatively converted to antimonial catechol. The fluoride crystallizes in white platelets sparingly soluble in water which do not melt or decompose below 300°.

Preparation of the Sodium Salt of Antimonial Catechol Thiosalicylic Acid.—Catechol (0.25 mole) was converted into antimonial catechol by one of the previously described procedures. The moist product was added in small portions with rapid agitation to a solution of thiosalicylic acid (42.4 g., 0.275 mole) in an equivalent of 2 N sodium carbonate and 50 cc. of water. The mixture was kept near the boiling point and 1 N sodium bicarbonate was added as required to keep the solution alkaline to litmus paper. Stirring was continued one-half hour after the addition was completed. The suspension was filtered hot and the filtrate concentrated until crystallization commenced, 50% yield. Found: 30.0% Sb. (Calculated for sodium antimonial catechol thiosalicylate, o-C6H4O2SbSC6H4COONao: Sb, 30.0%.) Faintly yellow platelets, readily soluble in water, which do not melt below 300°. An aqueous solution of the salt has a pH of 7 to 7.5. Acidification promotes decomposition.

Preparation of the Sodium Salt of Antimonial Catechol Salicylic Acid.—This compound results when salicylic acid is substituted for thiosalicylic acid in the preceding preparation; 30% yield. Found: Sb, 31.4%. (Calcd. for the sodium salt of antimonial catechol salicylic acid,  $o-C_6H_4O_2SbOC_6H_4COONa-o$ : Sb, 31.3%.) White platelets, readily soluble in water, which do not melt below  $300^\circ$ . An aqueous solution of the salt has a pH of 7 to 7.5. Acidification promotes decomposition. The isomeric phydroxybenzoic acid similarly gave a product containing

<sup>(1)</sup> See U. S. P. 1,873,668 (Aug. 23, 1932); U. S. P. 1,549,154 (Aug. 11, 1925).

<sup>(2)</sup> H. P. Brown and J. A. Austin, J. Am. Vet. Med. Assoc., XCV, 566-9 (1939).

<sup>(3)</sup> Causse, Bull. soc. chim., [3] 8, 245 (1892).

<sup>(4)</sup> Determined by the potentiometric method of analysis of organic arsenicals of F. E. Cislak and C. S. Hamilton, THIS JOURNAL, **52**, 638 (1930).

<sup>(5)</sup> Determined by means of Parr bomb sodium peroxide fusion.

30.6% Sb, while the isomeric *m*-hydroxybenzoic acid gave an analogous product containing 30.1% Sb. These compounds are white platelets soluble in water not melting below  $300^{\circ}$ .

Antimonial Dithiocatechol.—Dithiocatechol was prepared by the method of Hartley and Smiles.<sup>6</sup> Because of the insolubility of dithiocatechol in water and in saturated sodium chloride solution the modified method of Caussé for the preparation of antimonial catechol was inapplicable. Suspension of dithiocatechol (0.02 mole) in a solution of antimony trifluoride (0.02 mole) in 30 cc. of water gave a yellow product which after three alternate washings with water and ether was found to contain 35.8% Sb, and 29.1% S. No halogen was present. This indicates that the product was tri-(dithiocatechol)-distibine,  $(o-C_6H_4S_2)_3Sb_2$ which has 36.6% Sb, and 29.0% S; 60% yield based on dithiocatechol; yellow microcrystalline solid not melting or decomposing below 250°.

A solution of antimony trichloride (0.02 mole) in benzene (50 cc.) was refluxed with a solution of dithiocatechol (0.03 mole) in benzene (15 cc.) for three hours. Upon cooling, crystals separated which contained halogen and 40.9% Sb (calculated for dithio antimonial catechol chloride,  $o-C_6H_4S_2SbC1$ : Sb, 41.0); 40% yield; m. p. 174–175°, with decomposition. (From the benzene filtrate of this reaction a small amount of material identical with that from dithiocatechol and antimony trifluoride was obtained.) Antimony tribromide reacts similarly but less satisfactorily. Found 33.0% Sb (calcd. for dithiocatechol antimony bromide,  $o-C_6H_4S_2SbBr$ : Sb, 35.6), m. p. 162–163° with decomposition. These dithiocatechol antimonial halides hydrolyze in water and weak alkaline solutions to antimonial dithiocatechol.

Treatment of an ethyl alcohol solution (50 cc.) of dithiocatechol (0.01 mole) with freshly precipitated antimony oxide (0.02 mole) under reflux gave a reaction mixture which upon extraction with hot ethyl alcohol gave a product containing 43.1% Sb (calcd. for antimonial dithiocatechol,  $o-C_{0}H_{4}S_{2}SbOH$ : Sb, 43.6); 45% yield; yellow microcrystalline powder which does not melt below  $300^{\circ}$ .

Attempted reactions of the dithiocatechol derivatives with sodium salicylate, sodium thiosalicylate, and similar compounds failed to yield products of consistent antimony contents.

Dithiocatechol Antimonial Tartrate.—An attempt to prepare antimonial dithiocatechol from dithiocatechol and potassium antimonial tartrate by an adaptation of the method used by Christiansen<sup>7</sup> for preparing antimonial derivatives of polyhydric phenols gave potassium dithiocatechol antimonial tartrate. Dithiocatechol (0.05 mole) dissolved in ethyl alcohol (50 cc.) was added in small portions to a rapidly stirred solution of potassium antimonial tartrate (0.05 mole) in water (250 cc.). After stirring for one hour the yellow microcrystalline (platelets) precipitate formed was collected, washed with water, alcohol, ether, and dried; 60% yield. The product contained 27.4% Sb and 13.7% S which corresponds to  $o-C_6H_4S_2SbO-CH(COH)CH(OH)COOK$  containing 27.1% Sb and 14.3% S. The compound does not melt below 250°. The product was dissolved in sodium carbonate solution (1 N) and then made just acid to litmus paper with dilute hydrochloric acid (1 N). This material contained 29.8% Sb and 15.1% S which corresponds to dithiocatechol antimonial tartrate,  $o-C_6H_4S_2SbOCH(COOH)CH(OH)-COOH$  containing 29.6% Sb and 15.6% S.

Antimonial Monothiocatechol o-Hydroxythiophenol.-Monothiocatechol (0.05 mole), prepared by the method of Haitinger,<sup>8</sup> was dissolved in ethyl alcohol (100 cc.) and refluxed for six hours with freshly precipitated antimony trioxide. Repeated extraction of the resultant suspension with ethyl alcohol yielded a product which after recrystallization from ethyl alcohol contained 33.1% Sb. (Calcd. for antimonial monothiocatechol o-hydroxythiophenol o-C6H4OSSbSC6H4OH-o: Sb, 32.8.) Faintly yellow platelets, which do not melt below  $250^\circ$ ; 25% yield based on monothiocatechol. Attempts to prepare antimonial thiocatechol or its monohalide derivatives all resulted in the formation of this product. Monothiocatechol does not react with potassium antimonial tartrate as does dithiocatechol.

## Summary

Soluble derivatives of antimonial catechol and antimonial dithiocatechol have been prepared. The yields described in the experimental part can be made nearly quantitative on the basis of the organic molecules employed by the use of a large excess of the antimony containing reagent. Excellent yields of the sodium salts described are indicated by analysis of their aqueous solutions for antimony when they are not isolated from the reaction solutions. Such solutions are suitable for therapeutic use.

The preparations of antimonial catechol from antimonial catechol fluoride, antimonial dithiocatechol chloride, antimonial dithiocatechol bromide, antimonial dithiocatechol, tri-(dithiocatechol)-distibine, dithiocatechol antimonial tartrate, antimonial monothiocatechol *o*-hydroxythiophenol, and sodium salts of antimonial catechol thiosalicylic acid, and antimonial catechol *o*-, *m*- and *p*-hydroxybenzoic acids, have been described.

Dithiocatechol is more reactive than catechol toward antimony halides and oxides tending to react with all three rather than only two of the antimony valences. This is in accord with the reactivity of dithiocatechol toward tin and other metals. Monothiocatechol appears to be intermediate to reactivity between catechol and dithiocatechol toward these antimony compounds.

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<sup>(6)</sup> Hartley and Smiles, J. Chem. Soc., 1821-8 (1926); (see also,

H. P. Brown and J. A. Austin, THIS JOURNAL, **62**, 673 (1940)). (7) Christiansen *ibid* **48**, 1265-1260 (1996)

<sup>(7)</sup> Christiansen, *ibid.*, **48**, 1365–1369 (1926).

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<sup>(8)</sup> L. Haitinger, Monatsh., 4, 166-175 (1884); see also K. W. Palmer, U. S. P. 2,004,728 (1935).