2. Isorotenone is formed by the action of sulfuric acid on rotenone, and yields a phenylhydrazone.

3. Rotenic acid, which is obtained by the fusion of rotenone with potash, has the formula $C_{12}H_{12}O_4$. It yields a monomethyl ester and a mononitro derivative.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NEBRASKA]

THE ACTION OF ALKYL CHLOROCARBONATES ON STIBANILIC ACID[1]

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Studies in the field of organic antimonials have been carried out in connection with investigations of protozoal diseases because in some of these diseases the antimonials appear to be of greater value than the arsenicals.

It was the object of this investigation to prepare some of the carbalkoxy derivatives of *p*-aminostibinic acid and to study some of their properties. Methyl, ethyl, propyl, *iso*propyl, butyl, *iso*butyl, β-chloro-ethyl and γ-chloropropyl chlorocarbonates were condensed with *p*-stibanilic acid. Only one of the products, *p*-carbethoxyaminophenylstibinic acid was found reported in the literature.[2]

Two general methods, with various modifications, have been used for the preparation of *p*-aminophenylstibinic acid or *p*-stibanilic acid from *p*-aminoacetanilide; the first, by diazotization of *p*-aminoacetanilide and subsequent addition to alkaline antimony trioxide;[3] the second, by formation of the double salt in acid solution[4] and its addition to a solution of sodium hydroxide.[5] In both cases the acetyl group was removed by hydrolysis with a 5% solution of sodium hydroxide.

In this study both of the above methods were tried in the preparation of *p*-stibanilic acid with about equal results. With either method several difficulties were encountered. Not only was the material hard to handle mechanically but the yields were low. In the method finally adopted *p*-amino-acetanilide was diazotized and slowly added to an alkaline solution of antimony trioxide containing a little glycerol. The foam which forms was kept down by vigorous stirring and by regulating the

[1] Some of the compounds described in this paper are being studied pharmacologically under the direction of Dr. A. S. Loevenhart, Department of Pharmacology, University of Wisconsin.

[2] Brachmachari, *Indian J. Med. Research*, **10**, 508 (1922).

[3] German patent 254,421 (1911).

[4] May and Gray, *J. Chem. Soc.*, 3174 (1926).

[5] Dunning and Reid, THIS JOURNAL, **48**, 2959 (1926); **49**, 2869 (1927).

addition of the diazonium solution. At the conclusion of the reaction, the crude *p*-acetylaminophenylstibinic acid was precipitated with dilute acetic acid, hydrolyzed with a solution of sodium hydroxide and the crude stibanilic acid precipitated with dilute acetic acid. The derivatives prepared from this crude acid always analyzed too high in antimony content and it was found necessary to purify the acid before making the chlorocarbonate derivatives.

The several carbamates were prepared by dissolving the purified stibanilic acid in a slight excess of *N* sodium carbonate solution and adding slowly a slight excess of the chlorocarbonate. Their sodium salts separated out from the sodium carbonate solution and were converted to the free acids by use of hydrochloric acid. These carbamates were almost colorless powders insoluble in benzene, water or dilute acids. Concentrated hydrochloric acid changed them into a tarry oil. They showed but slight solubility in dilute sodium hydroxide solution, their solubility decreasing with an increase in their carbon content.

When 4-carbo-β-chloro-ethoxy- and 4-carbo-γ-chloropropoxyaminophenylstibinic acids were heated with four equivalents of aqueous alkali, β- and γ-phenylstibino-alkylamino alcohols, respectively, were obtained as illustrated by the formation of the β-compound.

$$H_2O_3SbC_6H_4NH_2 \longrightarrow H_2O_3SbC_6H_4NHCOOCH_2CH_2Cl \longrightarrow H_2O_3SbC_6H_4N(COOCH_2CH_2) \longrightarrow H_2O_3SbC_6H_4NHCH_2CH_2OH$$

No attempt was made to isolate the substituted oxazolidone shown in the above formulation but it was no doubt formed as an intermediate product.

Experimental

***p*-Aminophenylstibinic Acid (*p*-Stibanilic Acid), $NH_2C_6H_4SbO_3H_2$.**—Ninety grams of *p*-amino-acetanilide was added to 600 cc. of boiling water and decolorized with charcoal. One hundred and forty-four cubic centimeters of concentrated hydrochloric acid was then added and the solution cooled to 0–5°, when white crystals of the hydrochloride separated out. This mixture was diazotized with a solution of 42 g. of sodium nitrite in 250 cc. of water. The nitrite solution was introduced through a capillary tube at the bottom of the beaker, with mechanical stirring. The diazotized solution was then slowly added through a capillary tube to a jar containing a cold alkaline solution of antimony trioxide, prepared by dissolving 150 g. of antimony trichloride or 80 g. of antimony trioxide in a small amount of warm concentrated hydrochloric acid and 200 cc. of glycerol and adding this solution to just sufficient 5 *N* sodium hydroxide to dissolve the oxide that forms, followed by dilution with ice and water to eight liters. By regulating the addition of the diazonium solution and by vigorously stirring the mixture, a heavy foam which tends to form was prevented. During the addition of the diazonium solution the antimony trioxide was kept in solution by adding 10% sodium hydroxide solution from time to time as needed. When the reaction was complete the mixture was almost neutralized with hydrochloric acid and saturated with carbon dioxide to precipitate the unchanged antimony trioxide and tarry products. Before filtering the mixture was heated to 75° to coagulate the precipitated products; otherwise the finely

divided particles clogged the filter paper and a considerable time was required to filter. After filtering the *p*-acetylaminophenylstibinic acid was precipitated from the warm solution with dilute acetic acid and filtered. The acetyl group was removed by hydrolysis during one hour, in 1 liter of 5% sodium hydroxide solution at 90°. The crude acid was precipitated with acetic acid. The yields varied from 35 to 50%.

Purification of Stibanilic Acid.—Purification was accomplished by adding the moist crude acid, in small portions, to ice-cold, concentrated hydrochloric acid and stirring into a paste. After standing for a short time, the tetrachloride thus formed was filtered, washed with cold, concentrated hydrochloric acid and dissolved in just the required amount of 10% sodium hydroxide. This solution was warmed to 90°, decolorized with charcoal and the stibanilic acid precipitated with dilute acetic acid. To obtain a pure product consistently the process as outlined above was repeated. Yields of the purified acid were low and varied from 8 to 15% based on the crude acid.

Preparation of Alkyl and Chloro-alkyl Chlorocarbonates.—Following the method of Rose[6] these were prepared from the corresponding alcohols and phosgene at 0°.

Carbo-alkoxy-aminophenylstibinic Acids.—Purified *p*-stibanilic acid was dissolved in a slight excess of *N* sodium carbonate solution. To this solution a slight excess of the alkyl or chloro-alkyl chlorocarbonate was added, drop by drop, the reaction mixture frequently being shaken. The sodium salt of the carbo-alkoxy-aminophenylstibinic acid soon began to separate but the reaction mixture was allowed to stand overnight. The sodium salt was filtered off and suspended for a time in *N* hydrochloric acid to convert it into the free acid. The carbo-alkoxyaminophenylstibinic acid was washed with 2 *N* hydrochloric acid, to insure complete removal of any unchanged *p*-stibanilic acid, and then with water. When dried over sulfuric acid in a vacuum an almost colorless powder was obtained.

TABLE I

YIELDS AND ANALYTICAL DATA

4-Carbo-( )-aminophenylstibinic acid	Yield, %	Analysis: Subs., g.	0.0559 *N* I_2, cc.	Sb, % Calcd.	Sb, % Found
Methoxy, $CH_3OCONHC_6H_4SbO_3H_2$	73	0.1582	17.40	37.83	37.45
Ethoxy, $C_2H_5OCONHC_6H_4SbO_3H_2$	85	.1790	19.10	36.25	36.33
Propoxy, $CH_3CH_2CH_2OCONHC_6H_4SbO_3H_2$	87	.1573	15.93	34.80	34.48
*Iso*propoxy, $(CH_3)_2CHOCONHC_6H_4SbO_3H_2$	89	.1602	16.47	34.80	35.01
Butoxy, $CH_3CH_2CH_2CH_2OCONHC_6H_4SbO_3H_2$	70	.1577	15.46	33.46	33.38
*Iso*butoxy, $(CH_3)_2CHCH_2OCONHC_6H_4SbO_3H_2$	85	.1616	15.97	33.46	33.66
β-Chloro-ethoxy, $ClCH_2CH_2OCONHC_6H_4SbO_3H_2$	Good	.1576	16.02	32.88	34.61
γ-Chloropropoxy, $ClCH_2(CH_2)_2OCONHC_6H_4SbO_3H_2$	Good	.1579	14.68	31.68	31.66

***p*-Stibino-phenylamino Alcohols.**—One molecular equivalent of the 4-carbo-β-chloro-ethoxy- or 4-carbo-γ-chloropropoxy-aminophenylstibinic acid was suspended in 4 molecular equivalents of a 5% aqueous solution of sodium hydroxide and heated on a water-bath at 70–75°, with occasional stirring, for about thirty minutes. The gummy material which first formed soon dissolved, leaving a small residue of dark-colored material. Dilute acetic acid was then added until a precipitate just began to form. The mixture was decolorized with a small amount of charcoal, filtered and the amino alcohol precipitated with dilute acetic acid. The product was washed with a small amount of water and dried in a vacuum over sulfuric acid.

The amino alcohols thus produced were almost colorless powders, readily soluble in dilute alkali and soluble in hydrochloric acid.

[6] Rose, *Ann.*, **205**, 229 (1880).

TABLE II

YIELDS AND ANALYTICAL DATA

p-Aminophenylstibinic acid	%	Analysis Subs., g.	0.0606 *N* I_2, cc.	Sb, % Calcd.	Found
β-Hydroxy-ethyl-, $HOC_2H_4NHC_6H_4SbO_3H_2$	25	0.1592	17.28	39.55	40.05
γ-Hydroxypropyl-, $HOC_3H_6NHC_6H_4SbO_3H_2$	25	.1608	17.22	37.83	39.51

Determination of Yields.—Since *p*-stibanilic acid decomposes quite rapidly when dried, a weighed sample could not be used in making the derivatives and the yield directly calculated. The amount of acid used was determined by analyzing a 5-cc. aliquot taken with a pipet from the sodium carbonate solution used in the preparation of the derivatives, and from the amount of antimony in this sample the amount of stibanilic acid in the known volume of solution was determined.

Analytical

Different methods were tried for the analysis of these compounds and only fair agreement was obtained. A modification of the iodimetric method of Ewins[7] for arsenic was finally adopted.

A mixture of 0.2 g. of the substance, 10 g. of potassium sulfate and 0.2 to 0.3 g. of starch in a Kjeldahl flask was treated with 20 cc. of concentrated sulfuric acid and heated until colorless. At first a small flame was used, but after half an hour a much hotter one was applied. The clear solution was cooled, diluted with 100 cc. of water and made just alkaline with 10 *N* sodium hydroxide. In order to dissolve any precipitated oxide, tartaric acid was then added until the solution was faintly acid. To the cooled solution, solid sodium bicarbonate was added in excess, the solution diluted to 350 cc. and titrated with *N*/20 iodine solution using starch as the indicator. The iodine solution was standardized each time with a weighed sample of antimony trioxide using the above procedure. The pure antimony trioxide used for this standardization was prepared by precipitating it from a boiling solution of tartar emetic (1 part to 10 parts of water) with ammonium hydroxide. After boiling for a time the trioxide was filtered and carefully washed.[8]

Summary

1. Methyl, ethyl, propyl, *iso*propy., butyl, *iso*butyl, β-chloro-ethyl and γ-chloropropylchlorocarbonates have been condensed with stibanilic acid and the products isolated and identified (Table I).

2. The dried products were almost colorless powders, insoluble in water, dilute acids, benzene or ether. The methyl, ethyl and β-chloro-ethyl derivatives were slightly soluble in very dilute sodium hydroxide or carbonate solutions; the others were relatively insoluble. All were soluble in alcohol.

3. Two stibinophenylamino alcohols have been prepared (Table II).

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[7] Ewins, *J. Chem. Soc.*, **109**, 1356 (1916).

[8] L. Vanino, "Präparative Chemie," Vol. II, Ferdinand Enke, Stuttgart, p. 195.