and *p*-stibonobenzoic acids have not been previously described. *p*-Stibonophenoxyacetic acid has been reported by Brahmachari,[8] but no analyses were given. *m*-Stibonobenzoic acid apparently has been prepared by Dyson,[9] but the method of preparation was not mentioned nor were analyses given. The other stibonic acids listed have been prepared by other workers using the customary diazo procedure. Antimony was determined by titration with standard potassium bromate solution and the results reported are the average of two or more determinations.

Acknowledgment.—The authors wish to acknowledge the assistance given by Leon D. Freedman and David N. Kramer throughout the course of this work.

(8) Brahmachari, *Indian J. Med. Research*, **10**, 492 (1922).

(9) Dyson, *Rec. trav. chim.*, **57**, 1016 (1938).

Summary

A number of arylstibonic acids have been prepared by the Scheller reaction. Satisfactory results were obtained with aniline and its derivatives substituted in meta and para position, but not with derivatives substituted in ortho position. The majority of the stibonic acids prepared were purified by recrystallization of the corresponding pyridinium arylchloroantimonates. The latter compounds were found to give definite melting points which served to characterize the individual stibonic acids.

BALTIMORE 5, MD. RECEIVED MARCH 19, 1946

[CONTRIBUTION FROM THE VENEREAL DISEASE RESEARCH LABORATORY AND POSTGRADUATE TRAINING CENTER, U. S. PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

Some Reactions of Arylstibonic Acids

BY G. O. DOAK AND HARRY G. STEINMAN

The present communication describes the preparation of stibonic acids by reactions such as oxidation, esterification and ammonolysis, using as starting materials the stibonic acids prepared by the Scheller reaction and described in a previous paper.[1]

While such reactions have been used successfully for the preparation of arsonic acids, the metal–carbon bond is considerably weaker in the arylstibonic acids. In consequence, the resulting compounds are usually high in antimony, presumably due to rupture of the antimony–carbon bond during the reaction with the formation of inorganic antimony compounds. While many of these compounds could be purified by recrystallization of the corresponding pyridinium salts, this procedure was limited to compounds which did not disproportionate or hydrolyze under the conditions necessary for recrystallization, and was not applicable to many ortho substituted stibonic acids or compounds containing amide groups. Compounds in the latter class, prepared by ammonolysis of the corresponding esters, usually gave nitrogen analyses slightly lower than theoretical, presumably due to slight hydrolysis of the ester. No general method for purifying these compounds has been discovered. Where the pyridinium salts could be prepared and recrystallized, their melting points served to identify the individual stibonic acids and particularly to confirm the synthesis of the same compound by two or more different procedures.

Experimental

3-Nitro-*p*-toluenestibonic Acid.—*p*-Toluenestibonic acid (26.4 g., 0.1 mole), dissolved in 125 ml. of sulfuric acid was nitrated at 0–5° with a mixture of 7 ml. of sulfuric acid and 7 ml. of nitric acid (d. 1.14). The nitration mixture was poured onto ice and the resulting precipitate washed with water and purified through the pyridinium salt. The latter compound, when recrystallized from ethanol–hydrochloric acid (1:1), was identical (melting point, mixed melting point and analyses) with the pyridinium salt from the 3-nitro-*p*-toluenestibonic acid prepared by the Scheller reaction.

(1) Doak and Steinman, THIS JOURNAL, **68**, 1987 (1946).

Oxidation of Toluenestibonic Acids

***p*-Stibonobenzoic Acid.**—*p*-Toluenestibonic acid (26.4 g., 0.1 mole), was suspended in 500 ml. of hot water and 100 ml. of *N* potassium hydroxide, and oxidized at 80° with 35 g. of powdered potassium permanganate. The reaction was complete in two hours, when excess permanganate was destroyed with alcohol, the manganese dioxide removed by filtration and thoroughly washed with hot water. The impure *p*-stibonobenzoic acid, obtained by acidification of the combined filtrate and washings, was purified through the pyridinium salt. The latter compound was identical with the pyridinium salt from the *p*-stibonobenzoic acid prepared by the Scheller reaction.

2-Nitro-4-stibonobenzoic acid was prepared in a similar manner. The pyridinium salt was recrystallized without esterification from ethanol–hydrochloric acid.

The oxidation of *o*-toluene- and 6-nitro-*o*-toluenestibonic acids yielded principally antimony pentoxide.

The Esterification of Stibonobenzoic Acids

Methyl and Ethyl *p*-Stibonobenzoate.—The corresponding acids (20 g.) were suspended in 200 ml. of dry methanol at 0° and a stream of dry hydrogen chloride passed in for six hours. The resulting clear solutions were allowed to stand overnight at room temperature and then added to 3 liters of cold water to precipitate the esters. **Methyl *m*-stibonobenzoate** was prepared from *m*-stibonobenzoic acid (10 g.) by refluxing in methanol solution (100 ml.) for fifteen minutes, using sulfuric acid (10 g.) as a catalyst. The ester was precipitated from solution by the addition of water. The purification of all three esters described above was effected through the corresponding pyridinium salts.

A third method for preparing carboxy esters of stibonic acids has been found which is simple and of general applicability. The pyridinium salt of the corresponding stibonobenzoic acid was dissolved in warm methanol- or ethanol–hydrochloric acid mixture. The pyridinium salt of the ester separated from solution on cooling, and was readily converted to the desired ester stibonic acid by hydrolysis. The methyl and ethyl esters of both *m*- and *p*-stibonobenzoic acids have been prepared in this manner.

TABLE I

STIBONIC ACIDS AND THE CORRESPONDING PYRIDINIUM ARYLCHLOROANTIMONATES

Stibonic acid	Yield, %	Formula	Sb analyses, % Calcd.	Sb analyses, % Found	N analyses, % Calcd.	N analyses, % Found	Pyridinium arylchloroantimonate Formula	M. p., °C.[a]	Sb analyses, % Calcd.	Sb analyses, % Found	Cl analyses,[b] % Calcd.	Cl analyses,[b] % Found
3-Nitro-*p*-toluene	83	$C_7H_8NO_5Sb$	39.6	39.6	4.55	4.51	$C_{12}H_{12}Cl_5N_2O_2Sb$	191	23.6	23.8	34.4	34.5
p-Carbamylbenzene-	85	$C_7H_8NO_4Sb$	41.7	41.5	4.80	4.76	[c]					
p-Dimethylcarbamylbenzene-	97	$C_9H_{12}NO_4Sb$	38.1	38.2	4.38	4.25	[c]					
p-(β-Hydroxyethyl)-carbamylbenzene-	62	$C_9H_{12}NO_5Sb$	36.3	35.6	4.17	4.16	[c]					
p-Carbamylmethoxybenzene-	90	$C_9H_{10}NO_5Sb$	37.9	37.8	4.35	4.20	[c]					
p-Aminobenzene-[g]	62	$C_6H_8NO_3Sb \cdot H_2O$	43.2	44.4	4.97	4.89	[c]					
p-Acetamidobenzene-[h]	41	$C_8H_{10}NO_4Sb \cdot H_2O$	37.6	38.0	4.32	4.35	[c]					
p-Benzamidobenzene-	73	$C_{13}H_{12}NO_4Sb \cdot H_2O$	31.5	32.2	4.63	4.59	$C_{18}H_{16}Cl_5N_2OSb$	159	21.2	22.3	30.9	31.2
p-(*p*-Hydroxyphenylazo)-benzene-[i]	63	$C_{12}H_{11}N_2O_4Sb \cdot H_2O$	31.5	31.3	7.22	7.15	$C_{17}H_{15}Cl_5N_3OSb$	175	21.2	21.9	30.8	30.4[d]
p-Cyanobenzene-	40	$C_7H_6NO_3Sb \cdot H_2O$	41.7	41.5	4.80	4.80	$C_{12}H_{10}Cl_5N_2Sb$	161	25.3	25.7	36.9	36.4[d]
Methyl *p*-stibonobenzoate	85[e] 60[f]	$C_8H_9O_5Sb \cdot H_2O$	37.5	37.5			$C_{13}H_{13}Cl_5NO_5Sb$	217	23.7	24.0	34.5	34.5
Ethyl *p*-stibonobenzoate[j]	90[e] 60[f]	$C_9H_{11}O_5Sb \cdot H_2O$	36.0	36.2			$C_{14}H_{15}Cl_5NO_2Sb$	187	23.1	23.0	33.6	33.2
Methyl *m*-stibonobenzoate	85[e] 70[f]	$C_8H_9O_5Sb$	39.7	39.9			$C_{13}H_{13}Cl_5NO_5Sb$	195	23.7	23.9	34.5	34.7
Ethyl *m*-stibonobenzoate	70[f]	$C_9H_{11}O_5Sb$	38.0	38.0			$C_{14}H_{15}Cl_5NO_2Sb$	148	23.1	23.1	33.6	33.8
Methyl *p*-stibonophenoxyacetate	66[e] 90[f]	$C_9H_{11}O_6Sb$	36.2	35.7			$C_{14}H_{15}Cl_5NO_3Sb$	199	22.4	22.3	32.6	32.1
2-Nitro-4-stibonobenzoic	39	$C_7H_6NO_7Sb$	36.1	36.0	4.14	4.03	$C_{12}H_{10}Cl_5N_2O_4Sb$	186	22.3	22.2	32.5	32.2

[a] Melting points were taken by the method described in a previous paper from this Laboratory (THIS JOURNAL, **66**, 192 (1944)). [b] Chloride analyses were obtained by alkaline hydrolysis and subsequent titration with standard silver nitrate. In the few cases where this method gave unsatisfactory results the method of Willard and Thompson was used (THIS JOURNAL, **52**, 1893 (1930)). [c] Pyridinium salts of these compounds could not be prepared. [d] Chloride analysis by the method of Willard and Thompson. [e] Yield by the direct esterification of the corresponding stibonobenzoic acid. [f] Yield by esterification of corresponding pyridinium arylchloroantimonate. [g] *Cf.* references 3 and 4. [h] *Cf.* German Patent 254,421. [i] *Cf.* reference 4b, and Riddell and Basterfield, *Trans. Roy. Soc. Can.*, **23**, III, 45 (1929). [j] *Cf.* Riddell and Basterfield, reference *i*.

It was also found possible to convert from one ester to another by recrystallizing the corresponding pyridinium salt from a mixture of the appropriate alcohol and hydrochloric acid (1:1). The identity of the various ester stibonic acids prepared by the above methods was established by determining the melting points and mixed melting points of their pyridinium salts.

Methyl *p*-Stibonophenoxyacetate.—*p*-Stibonophenoxyacetic acid (22.6 g., 0.07 mole) was esterified in methanol solution with a stream of dry hydrogen chloride as described above. The clear solution was added to water, the small amount of gummy material which formed was removed, the solution neutralized with sodium hydroxide, and the precipitated ester purified through the pyridinium salt. The latter was also obtained from the pyridinium salt of stibonophenoxyacetic acid by crystallizing from methanol–hydrochloric acid mixture. Alkaline hydrolysis of this compound regenerated *p*-stibonophenoxyacetic acid, but the desired ester was readily obtained by dissolving the pyridinium salt in warm methanol and pouring this solution into sufficient water to precipitate the ester.

Ammonolysis of Ester Stibonic Acids

***p*-Carbamylbenzenestibonic Acid.**—Methyl *p*-stibonobenzoate (5.0 g.) was suspended in 100 ml. of concentrated ammonia water. After three days the clear solution was diluted with 200 ml. of water, excess ammonia removed *in vacuo*, and the stibonic acid precipitated by acidification with dilute hydrochloric acid. It was purified by triturating with concentrated hydrochloric as described in a previous paper.[2]

(2) *p*-Carbamylbenzenestibonic acid prepared by the Scheller reaction gave analytical values in agreement with the formula $H_2NCOC_6H_4SbO_4H_2 \cdot H_2O$, whereas the compound obtained by ammonolysis of the ester appeared to be anhydrous. Unfortunately, in this case the identity of the two compounds could not be established through the pyridinium salt, since under the conditions necessary for the preparation of the pyridinium salt the amide group was partially hydrolyzed. It is probable that one or both of these compounds were impure.

***p*-(Carbamylmethoxy)-benzenestibonic Acid.**—Methyl *p*-stibonophenoxyacetate (4 g.) was suspended in 80 ml. of cold aqueous ammonia, and the mixture allowed to remain in the ice box for one week. After dilution with 200 ml. of water, the stibonic acid was obtained by acidification with dilute hydrochloric acid.

***p*-Dimethylcarbamyl- and *p*-(β-hydroxyethylcarbamyl)-benzenestibonic acids** were prepared from methyl *p*-stibonobenzoate (10 g.) using 33% aqueous methylamine (100 ml.) and 35% aqueous 2-aminoethanol (200 ml.), respectively, in the manner described above.

Preparation of Amino- and Substituted Aminobenzenestibonic Acids

***p*-Aminobenzenestibonic Acid.**—*p*-Nitrobenzenestibonic acid (6.6 g., 0.02 mole) was suspended in 200 ml. of 0.1 *N* sodium hydroxide and the mixture shaken mechanically until a clear solution resulted. Reduction was then accomplished with Raney nickel and hydrogen at 40 lb. pressure, and was complete in from fifteen to thirty minutes. The reduction mixture had a distinct odor of aniline and fumed in the presence of hydrochloric acid. It was filtered into a flask surrounded with an ice–salt-bath and the filtrate acidified with cold 10% acetic acid. The stibonic acid which precipitated was washed with ice water and dried on a porous plate. It was obtained as a white powder which slowly darkened in the air.

Analytical values for antimony and nitrogen on different lots of *p*-aminobenzenestibonic acid prepared by this procedure showed variations of several per cent., with the nitrogen:antimony ratio always slightly less than unity. An attempt to purify this compound by treatment with ice-cold hydrochloric acid, as suggested by Schmidt,[3] failed to improve this ratio. It is difficult to understand how the more drastic synthesis of this compound by alkaline hydrolysis of *p*-acetamidobenzenestibonic acid at elevated temperatures could yield a pure compound.[4]

(3) Schmidt, *Ann.*, **429**, 123 (1922).

(4) (a) German Patent 270,448; (b) Dunning and Reid, THIS JOURNAL, **48**, 2959 (1926); (c) Hamilton and Etzelmiller, *ibid.*, **50**, 3360 (1928).

p-**Acetamidobenzenestibonic Acid.**—The clear solution obtained by the reduction of 6.6 g. of *p*-nitrobenzenestibonic acid, after removal of the catalyst, was shaken with acetic anhydride (25 ml.) for thirty minutes. Sufficient sodium hydroxide was added as necessary to keep the solution just alkaline. The stibonic acid was precipitated by acidification, and washed on a filter with 5% hydrochloric acid.

p-**Benzamidobenzenestibonic acid** was prepared in a similar manner from *p*-aminobenzenestibonic acid and benzoyl chloride. The acid was washed with 5% hydrochloric acid followed by alcohol and ether to remove any benzoic acid. The pyridinium salt after one recrystallization from ethanol–hydrochloric acid, gave analytical figures for antimony and chlorine which approached the theoretical values, but the higher analytical data on repeated recrystallization indicated hydrolysis of the benzamide group.

p-(*p*-**Hydroxyphenylazo**)-**benzenestibonic Acid.**—The reduction mixture from 6.6 g. of *p*-nitrobenzenestibonic acid was acidified with 100 ml. of *N* hydrochloric acid and diazotized at 0°. The diazo solution was added dropwise to 2 g. of phenol dissolved in 10 ml. of *N* sodium hydroxide and 50 ml. of water. Sodium hydroxide solution was added when necessary to dissolve the precipitate which formed. The solution was allowed to stand overnight at 10°, filtered, the stibonic acid precipitated by acidification, and purified through the pyridinium salt. The pure stibonic acid was a pale orange powder.

p-**Cyanobenzenstibonic Acid.**—A solution of diazotized *p*-aminobenzenestibonic acid (from the reduction of 13.2 g., 0.04 mole of *p*-nitrobenzenestibonic acid) was neutralized with sodium carbonate at 0°, and added to an excess of freshly prepared cuprous cyanide solution. After all the nitrogen was evolved the mixture was allowed to stand for twenty-four hours, filtered, and the filtrate acidified with dilute hydrochloric acid. The crude stibonic acid which precipitated was converted to the pyridinium salt and recrystallized several times from ethanol–hydrochloric acid. The free acid was then obtained by alkaline hydrolysis.

Table I lists the stibonic acids prepared, together with the corresponding pyridinium salts.

Acknowledgment.—The authors wish to acknowledge the assistance given by David N. Kramer throughout the course of the work.

Summary

The chemical nature of various substituted arylstibonic acids has been modified by reactions which include oxidation of tolyl groups, reduction of nitro groups, esterification, and ammonolysis. The resulting stibonic acids, which are usually contaminated with inorganic antimony compounds, can often be effectively purified by recrystallization of the corresponding pyridinium salts.

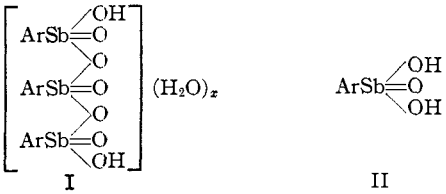
BALTIMORE 5, MD. RECEIVED MARCH 19, 1946

[CONTRIBUTION FROM THE UNITED STATES PUBLIC HEALTH SERVICE VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, JOHNS HOPKINS HOSPITAL]

The Structure of Arylstibonic Acids

BY G. O. DOAK

While a large number of arylstibonic acids have been described in the literature, the chemical structure of these compounds has not been established with certainty. On the basis of (1) analytical results, (2) their behavior as pseudo acids, and (3) the differences in weight loss obtained on thermal and vacuum drying, Schmidt[1] concluded that the arylstibonic acids existed in the solid state as trimers (I), but dissociated in alkaline solution to the salt of the orthoantimonic form (II), and that the number of associated water molecules (x in formula I) varied not only with different compounds, but with the same compound prepared by different procedures.



I

II

Further evidence for this hypothesis was advanced by Fargher and Gray[2] who prepared neutral sodium salts of these acids with a sodium: antimony ratio of less than unity.

(1) Schmidt, *Ann.*, **421**, 174 (1920); *Ber.*, **55**, 697 (1922).

(2) Fargher and Gray, *J. Pharmacol.*, **18**, 353 (1922).

While Schmidt's conception has been generally accepted, Macallum,[3] on the basis of molecular weight determinations in solution, concluded that these compounds possessed the monomolecular structure (II). The experimental evidence has been summarized by Christiansen[4] and Goddard,[5] both of whom favor Schmidt's conception.

In the two preceding papers[6] new methods for the preparation and purification of arylstibonic acids have been described. By recrystallization of the corresponding pyridinium salts, followed by alkaline hydrolysis, one regularly obtained compounds of fixed composition, independent of the method of preparation or isolation. With compounds which could not be purified through the pyridinium salts, the analytical figures usually showed considerable variation. In general,

(3) Macallum, *J. Soc. Chem., Ind.*, **42**, 468 T (1923).

(4) Christiansen, "Organic Derivatives of Antimony," The Chemical Catalog Co., New York, N. Y., 1925. This review, however, contains an error, pp. 60–61, where it is stated that the formula $[3(C_6H_5SbO_2)H_2O]\cdot 3H_2O$ used by Schmidt could be written as $C_6H_5SbO_3H_2\cdot H_2O$ without altering the proportions of the constituents. Internal evidence in Schmidt's paper, however, indicates that the factor 3 was not meant to apply to the following H_2O, and that the formula as postulated by Schmidt should be written $C_6H_5SbO_3H_2\cdot {}^1/_3H_2O$.

(5) Goddard, "A Text-book of Inorganic Chemistry," Vol. XI, part III, Charles Griffin and Co., Ltd., London, England.

(6) Doak and Steinman, THIS JOURNAL, **68**, 1987, 1989 (1946).