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ARTICLE No. 14.

A contribution to the Chemistry of certain new aromatic Antimonials.

UPENDRA NATH BRAHMACHARI and JNANENDRA MOHAN DAS GUPTA.

The study of organic antimonials has not been so exhaustive as that of organic arsenicals. In recent years some new organic pentavalent antimonials have been prepared and notable among these is urea stibamine discovered by one of us (U.N.B.), which has been found to be of great therapeutic value in the treatment of kala-azar. The reason why much less work has been done with organic antimonials than with arsenicals can be traced mainly to two important causes. First of all, organic antimony compounds are very difficult to prepare and are with few exceptions not crystalline. Secondly, most of them are unstable. This instability limits the formation of various complex antimonials, which has been possible in the case of arsenic. This is especially the case with stibino-benzene compounds as compared with arseno-benzene compounds. Generally speaking, in the case of arsenic, antimony, and bismuth this instability increases as the metallic character of the element becomes more and more pronounced. Thus C-Bi link is less stable than C-Sb link and C-Sb link less stable than C-As link.

The great difficulty involved in the preparation of aryl antimonials is really a barrier against extensive investigations on this type of compound. This difficulty becomes still greater, as minute impurities and slight variations of physical influences affect the stability of the compounds to a considerable extent, thereby bringing about marked changes in their toxicities and therapeutic properties.

In the Indian Journal of Medical Research, the Indian Journal of Medicine, and the Calcutta Medical Journal a series of new organic antimonials were described sometime ago by one of us and some of these compounds have been shown to be of great therapeutic value (U.N.B). Another series of new aromatic antimonials have since been investigated by us in the Brahmachari Research Institute and the following are the first series of such compounds:

1. Disodium p-aminophenyl stibinate-N-methylene sulphonate,
2. Urea-p-amino-phenyl stibinate-N-methylene sulphonate of sodium,
3. Disodium p-stibinilate-N-methylene-sulphinate,

4. Urea p-amino-phenyl stibinate-N-methylene sulphinate of sodium,
5. P-acetyl-amino-phenyl-stibinate of urea,
6. 1-acetamino-2-azobenzene-4 : 4'-distibinate of sodium,
7. P-hydroxy-phenyl-stibinate of urea.

Some of these compounds as will be seen from their percentage composition given below exhibit strong polymerisation whereby three molecules associate together giving rise to more complex molecules.

EXPERIMENTAL.

(1) Disodium p-aminophenyl stibinate-N-methylene sulphonate $3(4\text{-}SO_3Na.CH_2\text{-}NH.C_6H_4\text{-}SbO_2)H.ONa$.

The starting material in the preparation of this compound is stibanilic acid, which has been prepared by Bart's reaction. Stibanilic acid is neutralised with solution of sodium hydroxide and the sodium salt precipitated by absolute alcohol. The precipitate is then thoroughly washed with absolute alcohol till the filtrate is free from alkali. It is next dried in a vacuum dessicator.

Sodium stibanilate is dissolved in water and then formaldehyde solution and $NaHSO_3$ dissolved in water are added to it successively in a flask. The mixture is next heated on water-bath and filtered. The filtrate is treated with excess of alcohol when a bulky precipitate is produced which is washed with alcohol and dried in a porous plate in a vacuum dessicator.

The product is a light coloured powder—easily soluble in water to a perfectly clear solution which gives faintly acid test.

Composition :—

Dried material corresponds to the formula :

$(SO_3Na.CH_2.NH.C_6H_4.SbO)_3O_2(OH)(ONa)$.

$=C_{21}H_{22}O_{16}N_3S_3Sb_3Na_4$.

Calculated for $C_{21}H_{22}O_{16}N_3S_3Sb_3Na_4$—S=8.7%, N=3.8%, Sb=32.2%

Found S=8.5%, N=4.0%, Sb=32.5%

(2) Urea p-amino-phenyl-stibinate-N-methylene Sulphonate of sodium.

$3(4\text{-}SO_3Na.CH_2.NH.\ C_6H_4\text{-}SbO^2)H.OH_3N.CO.NH_2$.

The starting material in this preparation is urea stibamine. Urea stibamine is dissolved in a small quantity of water to which formaldehyde solution and $NaHSO_3$ dissolved in little quantity of water are added in succession. A bulky precipitate is formed on adding the constituents. The mixture is warmed on water bath. It is next filtered and the filtrate precipitated by alcohol. The precipitate is washed with absolute alcohol and then dried over a porous plate in a vacuum dessicator.

The product is a light coloured powder—easily soluble in water and giving a neutral test to litmus paper.

Composition :—

Dried material corresponds to the formula:

$SO_3Na,CH_2.NH.C_6H_4.SbO)_3O_2(OH)(ONH_3.CO.NH_2)$.

$=C_{22}H_{27}O_{17}N_5S_3Sb_3Na_3$.

Calculated for $C_{22}H_{27}O_{17}N_5S_3Sb_3Na_3$—S=8.29%, N=6.0%, Sb=31.1%

Found S=8.1%, N=6.3%, Sb=31.7%

(3) Disodium-p- stibanilate-N-methylene sulphinate.

$3(4\text{-}SO_2Na.CH_2.NH.C_6H_4\text{-}SbO_2)H.ONa$.

Stibanilic acid is treated with NaOH solution and the sodium salt next precipitated by adding absolute alcohol. The precipitate is washed with alcohol to remove the free alkali. The dried sodium salt is then dissolved in little water and the solution thus obtained treated with sodium formaldehyde sulphoxylate dissolved in little water. A bulky precipitate appears and the whole mixture is warmed on a water-bath when a clear solution is obtained with a small quantity of insoluble impurity. The solution after filtration is bit concentrated and then precipitated by absolute alcohol. The precipitate is next filtered and dried over a porous plate in a vacuum dessicator.

The product is a light coloured powder very soluble in water to a perfectly clear solution, giving a neutral test to litmus paper.

Composition :—

Dried material corresponds to the formula:

$(SO_2Na.CH_2.NH.C_6H_4.SbO)_3O_2(OH)(ONa)$.

$=C_{21}H_{22}O_{13}N_3S_3Sb_3Na_4$.

Calculated for $C_{21}H_{22}O_{13}N_3S_3Sb_3Na_4$—S=9.0%, N=4% Sb=33.7%

Found S=9.4%, N=4.2%, Sb=33.5%

(4) Urea p-amino-phenyl stibinate-N-methylene sulphinate of sodium.

$3(4\text{-}SO_2Na.CH_2,NH.C_6H_4.SbO_2)H.ONH_3.CO.NH_2$.

Urea stibamine is dissolved in water to which a solution of sodium formaldehyde sulphoxylate is added. A bulky precipitate appears and the whole mixture is well shaken. The mixture is next warmed on a water-bath. A clear solution with a slight sediment at the bottom is obtained which is next filtered. The clear filtrate after concentration is precipitated in cold by absolute alcohol. The precipitate is washed with alcohol, and dried over porous plate in a vacuum dessicator.

The product is a light coloured powder—readily soluble in water to a perfectly clear reddish solution which is faintly acid to litmus paper.

Composition :—

Dried material corresponds to the formula :

$(SO_2Na.CH_2.NH.C_6H_4.SbO)_3O_2(OH)(ONH_3.CO.NH_2).$

$= C_{22}H_{27}O_{14}N_5S_3Sb_3Na_3.$

Calculated for $C_{22}H_{27}O_{14}N_5S_3Sb_3Na_3$ – S = 3.65%, N = 6.3%, Sb = 32.4%

Found S = 3.4%, N = 6.0% Sb = 32.0%

(5) P-acetyl-amino-phenyl-stibinate of urea.

$3(4\text{-}CH_3CO.NH.C_6H_3.SbO_2)H.ONH_3.CO.NH_2.$

The starting material in this preparation is p-acetyl-amino-phenyl stibinic acid which is obtained from the corresponding acetyl phenylene diamine. The acid is thoroughly washed and the pasty mass is obtained in a semi-dry state by pressing over porous plate. The moist acid is treated with a little urea and then well mixed. The mixture is heated in boiling water when a reddish solution is obtained. A little more water may be added, if necessary, to obtain a clear solution and then warmed. The solution is next filtered through fluted filter paper and the filtrate precipitated by absolute alcohol. The precipitate is well washed with the same and dried over porous plate in a vacuum dessicator.

The product is a yellowish powder and dissolves in water to a clear solution, which is faintly acid.

Composition :—

Dried material corresponds to the formula :

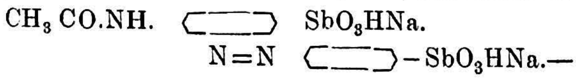
$(CH_3.CO.NH.C_6H_4.SbO)_3O_2.\ (OH)\ (O.NH_3.CO.NH_2).$

$= C_{25}H_{30}O_{11}N_5Sb_3.$

Calculated for $C_{25}H_{30}O_{11}N_5Sb_3$—N = 7.48%, Sb = 38.4%

Found N = 7.9%, Sb = 38.0%

(6) 1-acetamino-2-azobenzene-(4 : 4′)-distibinate of sodium.



The starting materials in the preparation of this compound are acetyl stibanilic acid and stibanilic acid. The former is obtained from acetyl-p-phenylene diamine and the latter by its hydrolysis with alkali. The stibanilic acid is partially dried on a porous plate and suspended in a small quantity of water. The mixture is cooled and treated with excess of H_2SO_4 when a clear solution is obtained. Acetyl stibanilic acid dried similarly is weighed and then dissolved in excess of alkali. The former acid solution is then gradually treated with $NaNO_2$ solution till it gives a blue coloration with the starch-iodide paper. The alkaline solution of the acetyl stibanilic acid is also cooled in ice and then gradually added to the diazotised solution. It is then filtered after allowing the little quantity of froth to escape. The sodium salt is then precipitated from the concentrated solution by absolute alcohol—dried over porous plate in a vacuum dessicator. ...

The product is a brown powder, dissolving in water to a clear red solution with neutral test.

Composition :—

Dried material.

Calculated for $C_{14}H_{13}O_7N_3Sb_2Na_2$—N=6.76%, Sb=38.6%

Found N=7.0%, Sb=38.1%

(7) P-hydroxy-phenyl-stibinate of urea.

$4—OH.C_6H_4.SbO_3H.NH_3.CO.NH_2$.

P-stibanilic acid which is obtained from acetyl p-phenylene diamine is made into a thick paste with water and the excess of H_2SO_4 added, the mixture being cooled. A solution is produced in this way which is well stirred while $NaNO_2$ solution is gradually added till it imparts blue colour to starchiodide paper immediately. The mass is next dissolved in alkali after gentle warming to liberate all nitrogen and filtered. The filtrate is reprecipitated with acetic acid. The mixture is filtered and well washed with water. The hydroxy-phenyl-stibinic acid thus obtained, which can also be directly obtained from p-aminophenol by applying Bart's reaction, is then well mixed with little excess of urea and heated on water bath when a red clear solution is obtained. It is then filtered and precipitated by acetone and dried in vacuo over porous plate.

The product is a yellow powder readily dissolving in water to a perfectly clear solution which is faintly acid to litmus paper.

Composition :—

Dried material.

Calculated for $C_7H_{11}O_5N_2Sb$—N=8.7%, Sb=37%

Found N=9%, Sb=37.6%

Therapeutic.

The therapeutic value of these compounds, if any, will be reported later on.

References.

(1) Indian Journal of Medical Research, Vol. X, No. 2, Oct. 1922; Vol. XI, No. 1, July 1923; Vol. XI, No. 11, Oct. 1923; Vol. XI, No. 4, April 1924; Vol. XII, No. I, July 1924; Vol. XII, No. 2, Oct. 1924; Vol. XII, No. 4, April 1925; Vol. XIII, No. 1, July 1925; Vol. XIII, No 3, January 1926.

(2) Indian Journal of Medicine, June 1926, Sep., 1926.

(3) Calcutta Medical Journal, June 1926, Aug., 1926.