ORGANO-METALLOID COMPOUNDS. PART II.

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Received April 10, 1936.

(Communicated by Sir C. V. Raman, Kt., F.R.S., N.L.)

In a previous communication,\(^1\) an attempt was made for preparing hydroxymethyl-phenyl-stibinic acids with a view to ascertain the physiological action, if any, of the hydroxymethyl group, in the treatment of Indian Kala-azar. From the published literature, it has been established that an antimonial, in order to be effective for the treatment of the disease caused by Leishmann-Donovann bodies, must confirm to the structure of 4-aminophenylstibinic acid. Relying on this observation, an attempt was made to prepare 5-amino 2-acetylaminobenzyl alcohol which by the application of well-known Bart-Schmidt reaction would give 2-acetylaminobenzylalcohol-5-stibinic acid. At the same time it was also considered to be of interest to investigate whether a stibinic acid with a CH\(_2\)OH group in \(-\ o\ -\) or \(-\ m\ -\)position exhibits any marked physiological activity.

5-Nitro-2-acetylaminobenzyl alcohol was prepared by the method of Cohn and Springer,\(^2\) from the acetyl derivative of 2-aminobenzaldehyde by nitration in sulphuric acid solution and Cannizaro's reaction, followed by subsequent acetylation. On reduction with iron and acetic acid, the nitro group was reduced to the amino body from which the stibinic acid was prepared as usual by diazo reaction. 3-Acetylaminobenzylalcohol-4-stibinic acid was prepared by the following series of reactions: 4-Nitro benzaldehyde, by Cannizaro's reaction, gave 4-nitrobenzyl alcohol which was smoothly reduced to the amino body in moist ether solution with Al-Hg couple. The method of reduction with zinc dust and calcium chloride\(^3\) was found to be a tedious one to work with. By heating with acetic anhydride and sodium acetate,\(^4\) a diacetyl derivative m.p. 102\(^\circ\) was obtained. On nitration with fuming nitric acid at 0-10\(^\circ\), 3-nitro-4-acetylaminobenzyl acetate was isolated in good yield, m.p. 82-83\(^\circ\). Deacetylation was effected as usual by heating with alcoholic sodium hydroxide. By diazotising the amino body in alcoholic

\(^1\) J. Indian Chem. Soc., 1931, 8, 59.
\(^2\) Monatsh., 1903, 24, 96.
\(^3\) Fischer, Ber., 1895, 28, 880.
hydrochloric solution and treating with antimony chloride, an additive compound of the diazonium chloride and antimony trichloride was obtained which was converted into the corresponding stibinic acid in pyridine solution (cf. Eng. Pat. 313,58 of 1928). After the reaction was over, the stibinic acid was isolated by dilution with water. The nitro-compound was reduced with ferrous hydroxide at 0–5° to 2-aminobenzylalcohol-4-stibinic acid, the acetyl derivative of which was prepared as usual.

The physiological action of the compounds described in the experimental part is now being investigated.

Experimental.

**Benzylalcohol-4-stibinic acid.**—4-Aminobenzyl alcohol (12.3 g.) was dissolved in hydrochloric acid (15 c.c., d. 1.12) and diazotised with a solution of sodium nitrite (6.9 g.) at 0°. To this solution was added a solution of antimony trichloride prepared by dissolving antimony trioxide (14 g.) in hydrochloric acid (30 c.c., d. 1.18). After being stirred for a minute or two, a white crystalline solid separated. This was filtered off, washed free from antimony trichloride with dilute hydrochloric acid (d. 1.12) and then with water. The solid was then suspended in water, cooled to a temperature of 5–10° and a dilute solution of caustic soda gradually added to the suspension, with vigorous mechanical stirring, till distinctly alkaline in reaction. Vigorous evolution of nitrogen occurred and the stirring gear was kept in motion till the evolution of nitrogen had slackened. The alkaline liquid was then nearly neutralised with dilute sulphuric acid and saturated with carbon dioxide. The whole was then filtered and the filtrate acidified with dilute acetic acid when the stibinic acid separated as a gelatinous precipitate. The stibinic acid was removed by centrifuging the liquid and freed from soluble inorganic impurities by dialysis. The insoluble impurities were then removed by dissolving the dialysed stibinic acid in dilute sodium carbonate solution and filtering off the insoluble impurities, if any. The slightly alkaline solution was then filtered and the pure stibinic acid precipitated by acidification with dilute acetic acid. The stibinic acid was then removed by filtration and washed repeatedly with water and alcohol till free from sodium acetate. It was then dried over fused calcium chloride in vacuo. [Found: C, 30.17; H, 3.42; Sb, 43.21%. \( \text{C}_7\text{H}_9\text{O}_4\text{Sb} \) requires C, 30.32; H, 3.25; Sb, 43.32 %.]

The sodium salt was prepared by dissolving the acid in the requisite quantity of dilute caustic soda, concentrating the solution in vacuo and precipitating the solution with a mixture of alcohol and ether. Light pink amorphous solid, decomposing on heating to 220° without melting. Very soluble in water. [Found: Na, 7.75 %; \( \text{C}_7\text{H}_9\text{O}_4\text{SbNa} \) requires Na, 7.68 %.]
Insoluble calcium and barium salts may be prepared by adding calcium or barium chloride to a solution of the sodium salt.

**Benzylalcohol-3-stibinic acid.**—This compound was prepared in the manner as described in the previous paragraph, from 3-aminobenzyl alcohol.

The sodium salt was prepared by dissolving the stibinic acid in dilute caustic soda and evaporating it to dryness in vacuo. The dry residue was then extracted with methyl alcohol or acetone, filtered and the filtrate treated with excess of ether when the sodium salt separated as a light pink amorphous mass. Filtered and dried in vacuo over liquid paraffin. [Found: C, 28.24; H, 2.82; Sb, 43.32; Na, 7.61%; \( \text{C}_7\text{H}_8\text{O}_4\text{SbNa} \) requires C, 28.09; H, 2.67; Sb, 43.47; Na, 7.68%]

**Benzylalcohol-2-stibinic acid.**—[Found: C, 30.31; H, 3.67; Sb, 43.33%.

**5-Amino-2-acetylaminobenzyl alcohol.**—Reduced iron dust (10 g.), acetic acid (4 c.c.) and water (50 c.c.) were placed in a round bottomed flask. 5-Nitro-2-acetylaminobenzyl alcohol (10 g.) was gradually added to the mixture with vigorous stirring. The mixture warmed up and the temperature rose up to 50°. Further quantities of the nitro-compound was gradually added to this warm mixture during 60 minutes. After about two hours, the flask was warmed on a water-bath and a dilute solution of sodium carbonate (2 g.) in water (20 c.c.) was added. The sludge was filtered off with suction and the residue repeatedly extracted with hot water. The filtrate immediately deposited a crystalline solid which was filtered off and dried in vacuo. It was then crystallised from alcohol-benzene mixture, in glistening plates, m.p. 172-73°. [Found: N, 15.62; \( \text{C}_9\text{H}_6\text{O}_2\text{N}_2 \) requires N, 15.73%]

**2-Acetylaminobenzylalcohol-5-stibinic acid.**—The amino body (8 g.) was dissolved in dilute hydrochloric acid (40 c.c., d. 1.12), cooled to 0° and diazotised with sodium nitrite. To this cooled diazo solution, under vigorous agitation, was added an alkaline solution of sodium antimonite prepared by dissolving antimony trioxide (5 g.) in hydrochloric acid (15 c.c.) and treating with a concentrated solution of caustic soda (30 c.c. 1:1). After the vigorous evolution of nitrogen had ceased the liquid was nearly neutralised with dilute sulphuric acid, saturated with carbon dioxide for 15 minutes and filtered. The filtrate was concentrated to about half its volume in vacuo over sulphuric acid and salted out when the sodium salt of the stibinic acid separated as a light red flocculent precipitate. This was filtered off, dried in vacuo over fused calcium chloride, dissolved in absolute methyl alcohol and precipitated by the addition of dry ether as a colourless amorphous mass. Yield 2 g. The precipitate was filtered and dried in vacuo.
over liquid paraffin. [Found: C, 30.23; H, 3.31; N, 3.63; Sb, 30.75; 
Na, 6.56 %. \( \text{C}_6\text{H}_5\text{O}_4\text{NSbNa} \) requires C, 30.34; H, 3.09; N, 3.91; 
Sb, 30.9; Na, 6.46 %.
]

**Properties.**—Amorphous mass with a pale pink colour. Decomposes on 
heating at 240°, without melting. Soluble in water and the free acid is 
precipitated by acidification and redissolved by alkali. The dried sodium 
salt is soluble in cold methyl alcohol. Insoluble in dilute mineral acids and 
other organic solvents.

The calcium or barium salt is precipitated as a white amorphous mass 
when calcium or barium chloride is added to a solution of the sodium salt.

**3-Nitrobenzylalcohol-4-stibinic acid.**—The starting material is 3-nitro-
4-aminobenzyl alcohol which was prepared by the method of Fourneau and 
Lestrange.\(^4\) Owing to the difficulty of diazotising this amine by ordinary 
method\(^4\) the base (10 g.) was dissolved in alcoholic hydrochloric acid, cooled 
in ice to 0° and treated with the necessary quantity of amyl nitrite. The 
solid diazonium chloride was then precipitated by the addition of ether and 
filtered off in the cold. It was then gradually added to a solution of antimony 
trichloride prepared by dissolving antimony trioxide (5 g.) in hydrochloric 
acid (15 c.c., d. 1.18). On stirring a colourless crystalline precipitate sepa-
rated. This was filtered off and dried carefully on a porous plate. The 
dry mass was then added in small quantities at a time to pyridine (50 c.c.) 
and stirred with a glass rod. The colour of the pyridine changed to red and the 
solid gradually went into solution. Brisk evolution of nitrogen was noticed 
and the temperature of the liquid went up to about 40-45°. After the addi-
tion of the whole of the solid, the solution was warmed on a water-bath to 
60°, till evolution of nitrogen had stopped (2 hours). A white solid was found 
to have separated. This was filtered off and found to be antimony trioxide. 
The clear liquid of a dark red colour was then diluted with water (500 c.c.) 
when a light pink gelatinous mass separated. This was filtered off and 
washed with dilute hydrochloric acid (d. 1.12) to remove antimony trioxide, 
if any, and then with water till free from acid. As the free stibinic acid is 
insoluble in organic solvents, it was purified through its sodium salt by pre-
cipitating a solution of the sodium salt in water with alcohol (twice). Finally 
it was dried in vacuo over fused calcium chloride (cf. Eng. Pat. 313,58 
of 1928). [Found: C, 24.51; H, 2.31; N, 3.88; Sb, 34.72 %. 
\( \text{C}_7\text{H}_5\text{O}_4\text{NSbNa} \) requires C, 24.42; H, 2.04 N, 4.08; Sb, 34.9 %.]

**3-Aminobenzyl alcohol 4-stibinic acid.**—To a solution of the sodium salt 
described above (8 g.) in \( n \)-caustic soda (100 c.c.), cooled to 0°, ferrous 
sulphate (50 g.) in water (100 c.c.) was added slowly with vigorous stirring, 
the temperature being maintained between 0 and 5°. \( n \)-Caustic soda (100 c.c.)
was added to the mixture to make it distinctly alkaline and the stirring continued for 4 hours. The sludge of ferric hydroxide was then removed by centrifuging the liquid and the residue was extracted twice with 100 c.c. of 2% caustic soda. The united filtrates were concentrated in vacuo and the sodium salt precipitated by the addition of alcohol. The crude sodium salt was then removed by filtration and again dried in vacuo. The dried mass was repeatedly extracted with acetone and filtered; the filtrate was concentrated in vacuo and then precipitated by the addition of ether. Finally the precipitated sodium salt was again dried in vacuo over calcium chloride—liquid paraffin. [Found: N, 4.25; Sb, 38.15 %. C₆H₆O₄NSbNa requires N, 4.45; Sb, 38.22 %.]

Properties.—The sodium salt is a yellowish white amorphous mass, decomposing at 230°, without melting. It is very soluble in water and fairly soluble in acetone. The free stibinic acid is obtained by acidification with dilute acetic acid and dissolves completely in dilute hydrochloric acid. Insoluble calcium salt is precipitated by adding calcium chloride to an aqueous solution of the sodium salt.

The acetyl derivative was prepared by warming the free stibinic acid (1 part) with twice the required quantity of acetic anhydride on a water-bath for a few minutes. On cooling the liquid, a precipitate separates which is filtered off and washed with hot water. The mass was then dissolved in sodium carbonate till just alkaline and again filtered from insoluble impurities, if any. The solution was then concentrated in vacuo over caustic soda and saturated with sodium chloride when the sodium salt separated as an amorphous mass. This was filtered off, dried in vacuo, dissolved in methyl alcohol and precipitated by the addition of ether, as a light red amorphous mass. [Found: N, 3.72; Sb, 33.56 %. C₆H₁₀O₅NSbNa requires N, 3.93; Sb, 33.7 %.]

The best thanks of the author are due to Prof. Dr. H. K. Sen for placing all the facilities of his laboratory at his disposal.