ORGANO-METALLOID COMPOUNDS. PART I.

BY SUDHIRCHANDRA NIVOGY.
(From the Department of Applied Chemistry, University College of Science and Technology, Calcutta.)

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UNTIL recently it was assumed that for the preparation of an active trypanocide (among arsenicals) the structure of the compound must correspond to the salvarsan type, i.e., the compound must be derived from 3-nitro-4-hydroxyphenylarsenic acid. In fact, any deviation from this type was attended with diminished activity or increased toxicity. It has been recently demonstrated by Albert\(^1\) that compounds having no similarity to salvarsan in structure, may also possess trypanocidal activity not inferior to salvarsan or its allied products. The substance in question is known as "Albert 102" having the following constitution:—

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\begin{align*}
\text{CH}_3 - &\text{C} = \text{N.NH\phi} \quad \text{CH}_3 - &\text{C} = \text{N.NH\phi} \\
\text{ONa} & \quad \text{ONa}
\end{align*}
\]

\((\phi = -\text{Ph or } -\text{CO.NH}_2)\)

The substance thus appears to be a semicarbazone or phenylhydrazone of the corresponding ketone. That either of these groupings may have any effect in the appearance of trypanocidal properties in an arsenical, is noticed for the first time in "Albert 102". The function of the hydroxyl group might be to render the product capable of forming soluble salts, since it has been found that acetophenone-4-arsenic acid has a therapeutic activity between 4 and 6.

As in the case of the trivalent arseno-compounds, the presence of amino and hydroxyl groups in particular positions were considered essential, so also in the case of the stibinic acids employed for the treatment of Indian Kala-azar, it is still maintained that therapeutically active compounds must be derived from 4-aminophenylstibinic acid. But considering the case of "Albert 102", the preparation of the corresponding stibinic acid was undertaken to find, whether it exhibits any activity or not; since however, the trivalent stibino-compounds are very unstable, the true antimony analogue of

\(^1\) Klin. Woch., 1924, 48, 2184.
"Albert 102", could not be prepared, the corresponding stibinic acid being the final product of this investigation.

For the preparation of semicarbazone of acetophenone 2-hydroxy-4-stibinic acid, an attempt was first made to prepare 2-hydroxy-4-aminophenyl methyl ketone by the nitration of 4-acetylaminacetophenone in sulphuric acid solution with nitric acid (d 1.40) but unfortunately this scheme could not be worked upon, as the isomeric 2-nitro- and 3-nitro-4-acetylaminacetophenone, which were produced simultaneously, could not be separated. The method that was finally adopted for the preparation of the required compound consisted in the preparation of 4-acetylaminacetophenone with some modification. Kunchell (loc. cit.) employed acetyl bromide, acetanilide and aluminium chloride. We substituted acetyl chloride for the bromide and succeeded in getting an excellent yield by adding the acid chloride to a mixture of acetanilide and aluminium chloride in dry carbon disulphide. When, however, aluminium chloride was added gradually to a mixture of the acid chloride and acetanilide in carbon disulphide, the reaction did not take place and unchanged acetanilide was obtained at the end of the operation. 4-Acetylaminacetophenone was then hydrolysed and the free amine diazotised in hydrochloric acid solution and treated with a solution of antimony trichloride in hydrochloric acid. It is generally found that an additive compound of the diazonium chloride and antimony trichloride separates at once but in this case, the additive compound was found to be rather soluble in hydrochloric acid and the concentration of the acid was carefully regulated so that no antimony oxychloride separated. After the usual alkaline decomposition of this additive compound at a low temperature, the free stibinic acid was isolated by acidifying the reaction liquid with dilute sulphuric acid (the stibinic acid is soluble in acetic acid). Acetophenone-4-stibinic acid (sodium salt) was dissolved in formic acid solution or in a mixture of acetic acid and formic acid and slowly added to concentrated sulphuric acid at 0–0.5° and then nitrated as usual. The nitrated product was collected as usual by diluting the acid solution with crushed ice. The nitrostibinic acid was found to be soluble in alcohol and the crude product was purified by dissolving in alcohol and precipitating the stibinic acid with water. The ketone was then converted into its semicarbazone and the nitro-group reduced, with aluminium mercury couple. The free ketone was then regenerated by warming with dilute hydrochloric

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2 Gibson and Levin, J. C. S., 1931, 2388.
3 Kunchell, Ber., 1900, 33, 2642.
4 D. R. P., 259,875; 287,709.
acid and the amino-group replaced by hydroxyl through diazo reaction. The keto group was again converted into its semicarbazone.

The constitution of the nitration product of acetophenone-4-stibinic acid, described before, is a matter of uncertainty. The orienting influence of both SbO₃H₂ and CO.CH₃ is meta. But in our experiments, the main product isolated is acetophenone-2-nitro-4-stibinic acid. The constitution of this was established by the following reactions:—Nitroacetophenone stibinic acid was treated with dilute sulphuric acid and potassium iodide when the antimony complex was removed and replaced by iodine, the product thus isolated being 2-nitro-4-iodoacetophenone. On oxidation with alkaline permanganate, -CO.CH₃ was converted into -COOH group giving 2-nitro-4-iodobenzoic acid. By distillation with soda lime, the carboxyl group was removed giving 3-nitroiodobenzene identical with an authentic sample in every respect. Thus it is clear that in this case the nitration product isolated by us is 2-nitro-acetophenone 4-stibinic acid.

The physiological action of the final product—semicarbazone of 2-hydroxy acetophenone-4-stibinic acid—was not satisfactory. The M. L. D. for white mice lies between 150 and 200 mg. per kg., but it was found to have only a slight action in cases of Kala-azar and that only in its early stages.

**Experimental.**

_4-Acetylaminoacetophenone._—This was prepared by a modification of the method described by Kunchell.⁵ To a mixture of acetanilide (10 g.) and anhydrous aluminium chloride (30 g.) in carbon disulphide (25 c.c.) under reflux, acetyl chloride (15 c.c.) was added gradually with vigorous agitation during 30 minutes. The reaction was then completed by heating on a water-bath for 1 hour and excess of carbon disulphide was distilled off. The dark red oily reaction product was then well cooled in ice and then treated with ice cold dilute hydrochloric acid. A pasty light brown solid was thus obtained which was filtered off and recrystallised from water (charcoal) as light brown crystals, m. p. 166-67°; yield 7.5 g.

_Hydrolysis._—The hydrolysis of the acetyl group was carried out according to the method of Kunchell (loc. cit.). The crude product was crystallised from water, in glistening yellow plates, m. p. 104-5°.

_Acetophenone-4-stibinic acid._—4-Aminoacetophenone (10 g.) was dissolved in water (30 c.c.) and hydrochloric acid (7.5 c.c.). The solution was cooled to 0° and diazotised with the addition of sodium nitrite (5 g.) in water (20 c.c.). A solution of antimony trichloride (7 g.) in hydrochloric acid (25 c.c.) was then

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⁵ Ber., 1900, 33, 2642.
gradually added to the diazzo solution and the precipitated yellowish white solid was filtered off, washed first with hydrochloric acid (d. 1.12) and then with water. The moist mass was then suspended in water, cooled to 10° and a solution of caustic soda added, under vigorous stirring, till faintly alkaline. After the evolution of nitrogen has slackened off (1 hour), the liquid was nearly neutralised with dilute sulphuric acid and saturated with carbon dioxide for 15 minutes. The dark coloured residue was filtered and the filtrate acidified with dilute sulphuric acid when the free stibinic acid separated as a light brown gelatinous mass. The precipitate was allowed to stand overnight in a refrigerator and filtered off. It was then suspended in water and dissolved by the gradual addition of dilute caustic soda till faintly alkaline. The alkaline solution was then evaporated to dryness in vacuo over sulphuric acid and the brown residue repeatedly extracted with methyl alcohol, filtered and the filtrate treated with excess of ether when the sodium salt separated as a light brown mass. This was again filtered off, washed with ether and dried in vacuo over liquid paraffin (yield 3 g.). [Found : C, 30.7; H, 3.12; Sb, 39.2%. C₈H₈O₄SbNa requires C, 30.9; H, 2.57; Sb, 38.58%.

Properties.—The sodium salt was a light red amorphous powder, decomposing between 220 and 40° without melting. It is very soluble in alcohol and a concentrated solution in water gave no precipitate when treated with large excess of alcohol. When an aqueous solution was first acidified with dilute sulphuric acid, the free stibinic acid separated which however dissolved in excess of dilute acetic acid. On the addition of barium or calcium chloride insoluble barium or calcium salt of the stibinic acid separated as an amorphous mass.

2-Nitro-acetophenone-4-stibinic acid.—Sodium salt of acetophenone-4-stibinic acid (5.5 g.) was dissolved in anhydrous formic acid (40 c.c.) and added very slowly to concentrated sulphuric acid (25 c.c.) cooled to 0°, with mechanical stirring. A mixture of nitric acid (1.5 c.c., d. 1.40) and sulphuric acid (10 c.c., d. 1.84) was then slowly added to the cooled sulphuric-formic acid solution of the stibinic acid at 0°-5° with gentle stirring. The stirring was continued for 60 minutes after the addition of the whole of the nitrating acid. The thick brown liquid was then poured into crushed ice (100 g.) when a light red gelatinous mass separated. The mass was separated by centrifuging the liquid and was washed free from acid with water. Contrary to our expectations, this stibinic acid was found to be rather soluble in alcohol and its purification was effected by dissolving the solid in rectified spirit and adding an excess of water when the free stibinic acid was precipitated (twice). Finally it was dried in vacuo over fused calcium chloride.
(yield 3.5 g.): [Found: N, 3.80; Sb, 35.7; C, 26.53; H, 2.85%.
CsH₉O₆NSb requires N, 4.1; Sb, 35.9; C, 26.98; H, 2.41%]

Properties.—The nitro-stibinic acid was found to be a light brown solid easily soluble in alkali or alkali carbonate and precipitated by the addition of mineral acids or acetic acid. On being heated with concentrated hydrochloric acid and then diluting and treating with sulphurated hydrogen, an orange precipitate of antimony sulphide was obtained. As stated before it was soluble in alcohol and insoluble in water. Insoluble calcium or barium salts were thrown down when a solution of the sodium salt was treated with calcium or barium chloride.

Semicarbazone of 2-nitro-acetophenone-4-stibinic acid.—The semicarbazone was prepared from the ketone by dissolving the nitroketonic stibinic acid in dilute caustic soda (avoiding excess) and warming on a water-bath for several hours with semicarbazide. A white precipitate of the antimony oxide separated during the heating and was removed by filtration. The free stibinic acid was then precipitated by adding dilute acetic acid, filtered and washed repeatedly with cold dilute hydrochloric acid to remove excess of semicarbazide. The sodium salt was then prepared as usual and was precipitated by the addition of alcohol (twice). Finally it was filtered off, washed and dried as usual in vacuo. [Found: N, 12.8; Sb, 28.70; C, 26.58; H, 3.2%. CsH₁₀O₆N₄SbNa requires N, 13.5; Sb, 29.05; C, 26.11; H, 2.52%]

Properties.—It is a light pink amorphous powder, freely soluble in water forming a red solution. On acidifying with dilute hydrochloric acid and adding sodium nitrite, copious evolution of nitrogen was noticed.

Semicarbazone of acetophenone 2-amino-4-stibinic acid.—The corresponding nitro compound (2 g.) was dissolved in water (50 c.c.) and gradually treated with aluminium mercury couple (4 g.) in the course of 4 hours. After standing overnight, the precipitated aluminium hydroxide was filtered off and the precipitate twice extracted with dilute sodium carbonate and the filtrate and the extracts saturated with carbon dioxide. After filtration from the separated solid, the clear liquid was acidified with dilute acetic acid when a gelatinous precipitate separated. On examination, this was found to be the desired product and was converted into sodium salt by treatment with the required quantity of sodium carbonate and the aqueous solution subsequently precipitated by alcohol when the sodium salt separated as a light pink amorphous mass (yield 1 g.). [Found: Sb, 31.67; C, 27.9; H, 3.6%. C₉H₂O₆N₂SbNa requires Sb, 31.33; C, 28.2; H, 3.1%]

Properties.—It is a faint pink powder, easily soluble in water to a red solution. When treated with dilute acetic acid, it gave a precipitate which
dissolved in dilute hydrochloric acid. It gives diazo reaction with evolution of nitrogen.

2-Aminoacetophenone 4-stibinic acid.—This was prepared from the above compound by splitting off the semicarbazide by heating with 25% hydrochloric acid. It was found however that a considerable part of the stibinic acid itself was decomposed during this heating, as the stibinic acids are unstable in presence of strong mineral acid. After filtering off the insoluble bye-products the liquid was cooled in a freezing mixture and treated with freshly prepared ice-cold fuming hydrochloric acid (d. 1.20) when a white precipitate separated. This was found to be hydrochloride of the amino body and was filtered off in the cold. It was then dissolved in a small quantity of ice cold water and saturated with sodium acetate when a precipitate separated which was found to be the required stibinic acid. Sodium chloride and excess of sodium acetate was removed by repeated washing with distilled water and the free stibinic acid was converted into sodium salt as described before. [Found: Sb, 35.2; C, 28.9; H, 3.25; N, 3.71%. \( \text{C}_8\text{H}_4\text{O}_4\text{NSbNa} \) requires Sb, 35.7; C, 29.4; H, 2.72; N, 4.3%]"}

Properties.—The sodium salt found to be soluble in water and in dilute mineral acids. It gave diazo reaction without evolution of nitrogen.

Semicarbazone of 2-hydroxy acetophenone 4-stibinic acid.—The regenerated aminoketone stibinic acid was dissolved in dilute hydrochloric acid, cooled to 0° and diazotised with the necessary quantity of sodium nitrite, the liquid was then allowed to stand at ordinary temperature till evolution of nitrogen had ceased (3 hours). A precipitate was found to have separated during this time, which was removed by filtration, washed and dissolved in dilute sodium carbonate. Semicarbazide (2 g.) was dissolved in water (10 c.c.) and neutralised with dilute alkali. The two solutions were mixed and heated on a water-bath at 60–80° for 2 hours and allowed to stand overnight. The liquid was then filtered, acidified with dilute hydrochloric acid and the resulting precipitate washed first with dilute hydrochloric acid and then with water. It was then converted into sodium salt as usual. [Found: N, 10.2; Sb, 30.9; C, 27.85; H, 3.2%. \( \text{C}_8\text{H}_11\text{O}_5\text{NSbNa} \) requires N, 10.9; Sb, 31.2; C, 28.13; H, 2.98%]

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