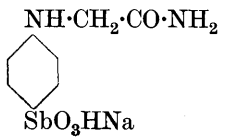
C.—*Aromatic Stibinic Acids containing Phenyl and Quinolyl Radicals.*

By GILBERT T. MORGAN and JAMES WILFRED COOK.

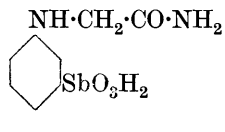
IN recent years considerable attention has been directed towards organic antimonials as therapeutic agents in tropical medicine (Schmidt, *Ind. Med. Gaz.*, 1928, **63**, 643) and the compounds now described were prepared in the course of a search for active substances of greater stability than *p*-aminophenylstibinic acid, from which many of the successful antimonials are derived.

One of the most promising arsenicals in present use is tryparsamide and Brahmachari (*Indian J. Med. Res.*, 1922, **10**, 510) claimed to have isolated the analogous antimony compound (sodium *N*-phenylglycineamide-*p*-stibinate, I). We have made repeated unsuccessful attempts to prepare Brahmachari's substance, the chief difficulty being that *p*-aminophenylstibinic acid decomposes rapidly under the conditions necessary to effect condensation with chloroacetamide. Attempts to overcome this difficulty by introducing the stibinic acid group into a previously formed *N*-phenylglycine molecule (for example, by the Bart–Schmidt reaction with *p*-amino-*N*-phenylglycine or *p*-amino-*N*-acetyl-*N*-phenylglycine) also proved abortive. Moreover, *pp'*-diaminodiphenylstibinic acid and 4-hydroxy-3-aminophenylstibinic acid both decomposed when heated with chloroacetamide in faintly alkaline solution.

m-Aminophenylstibinic acid is considerably more stable than its para-isomeride and condenses smoothly with chloroacetamide and with chloroacetomethylamide to yield N-*phenylglycineamide*-m-*stibinic acid* (II) and *N*-phenylglycinemethylamide-*m*-stibinic acid (III) respectively.



(I.)



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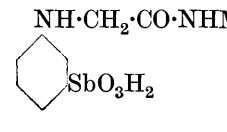
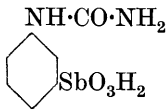


(III.)

m-Aminophenylstibinic acid also reacted with cyanic acid to give m-*carbamidophenylstibinic acid* (IV).

4-Chloro-3-aminophenylstibinic acid (V), obtained by oxidation of 4-chloro-3-aminophenylstibinous chloride hydrochloride (Schmidt, *Annalen*, 1920, **421**, 208; *Ber.*, 1926, **59**, 556) with ammoniacal hydrogen peroxide at 0°, failed to react when its sodium salt was heated with chloroacetamide or chloroacetomethylamide in aqueous or alcoholic solution, the reactivity of the primary amino-group being probably depressed by the ortho-chlorine atom.

The chlorine atom in 4-chloro-3-nitrophenylstibinic acid (Schmidt, *Annalen*, 1920, **421**, 188) is considerably less reactive than that in the analogous arsinic acid (D.R.-PP. 285,604, 446,545; Barber, J., 1929, 471), since it does not condense with pyridine or aniline at 100°, with ammonia at 120°, or with diethylamine in boiling alcoholic solution. With piperidine in boiling alcohol, however, 3-*nitro*-4-*piperidinophenylstibinic acid* was readily obtained, and this was reduced by ferrous hydroxide to 3-*amino*-4-*piperidinophenylstibinic acid* (VI).



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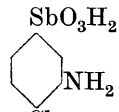

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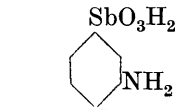
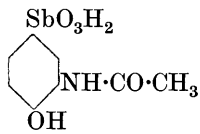
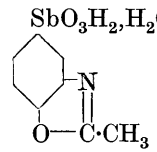


(VI.)

3-*Nitro*-4-*ethylaminophenylstibinic acid* was produced from 4-chloro-3-nitrophenylstibinic acid and ethylamine in alcoholic solution at 120—130°, the reaction being accompanied by partial elimination of antimony from the molecule.

Treatment of an aqueous suspension of 3-amino-4-hydroxyphenylstibinic acid with acetic anhydride led to the formation of a stibinic acid which was probably 3-*acetamido*-4-*hydroxyphenylstibinic acid* (VII), but its extreme solubility in water was remarkable, since most aromatic stibinic acids are very sparingly soluble, as is also the analogous arsinic acid (stovarsol), so the possibility of internal condensation to a benzoxazole derivative (VIII) is not excluded.

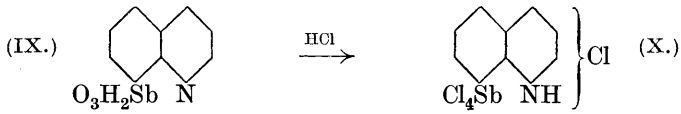
(VII.)




(VIII.)

The conditions necessary for the production of quinolylstibinic acids by the Bart–Schmidt reaction have been determined (compare Binz and Räth, *Eng. Pat.* 250,287) and *quinolyl*-5-*stibinic*, *quinolyl*-6-*stibinic*, and *quinolyl*-8-*stibinic acids* were obtained from the corresponding aminoquinolines. The stibinic acid group has less in-

fluence than the arsinic acid group in inhibiting the basic character of the quinoline residue, since these stibinic acids are soluble even in dilute acetic acid, whereas Binz and Räth (*Annalen*, 1927, **453**, 240) have shown that the corresponding arsinic acids require concentrated mineral acids for salt formation. These quinolylstibinic acids were purified through their sparingly soluble crystalline *stibinic chlorides*, the salt obtained from quinolyl-8-stibinic acid (IX), for example, being represented by structure X :



By evaporation of its solution in dilute acetic acid, quinolyl-8-stibinic acid (IX) is converted into a water-soluble variety which is probably a salt formed by internal neutralisation, since the isomeric 5- and 6-compounds do not behave in this way. An attempt was made to prepare 6-methoxyquinolyl-8-stibinic acid and 6-ethoxyquinolyl-8-stibinic acid from the corresponding alkoxyaminoquinolines, which themselves are stated to be destructive to blood parasites (*Eng. Pat.* 267,457). The yield of these stibinic acids was, however, very poor and they could not be obtained free from coloured impurities, but it is noteworthy that neither of these derivatives of quinolyl-8-stibinic acid could be converted into a water-soluble form by evaporation of dilute solutions of the acetates.

The trypanocidal action of the compounds now described has been examined by Professor Warrington Yorke under the auspices of the Chemotherapy Committee of the Medical Research Council. The substances were administered intraperitoneally and were found to possess only a slight activity against *T. equiperdum*. The minimum lethal doses (M.L.D.), expressed in mg. per 20 g. mouse, are given in the following table, sodium *m*-aminophenylstibinate being included for comparison.

Substance.	M.L.D.
Sodium *m*-aminophenylstibinate	25
Sodium *m*-carbamidophenylstibinate	25
Sodium *N*-phenylglycineamide-*m*-stibinate	20
Sodium *N*-phenylglycinemethylamide-*m*-stibinate	30
Acetylated 3-amino-4-hydroxyphenylstibinic acid (VII or VIII)	10
Sodium quinolyl-5-stibinate	1·8
Sodium quinolyl-6-stibinate	3·6
Quinolyl-8-stibinic acid	0·9

Experimental.

I. *Derivatives of* m-*Aminophenylstibinic Acid.*

m-*Carbamidophenylstibinic Acid* (IV).—*m*-Aminophenylstibinic acid (6 g.) was dissolved in *N*-hydrochloric acid (20 c.c.), and the

excess of mineral acid neutralised with sodium hydroxide. 2*N*-Acetic acid (25 c.c.) was added, followed by a concentrated aqueous solution of potassium cyanate (2·5 g.) at 0°. After an hour the precipitate was collected and reprecipitated by hydrochloric acid from its solution in sodium hydroxide. For purification, the product (5·5 g.) was suspended in concentrated hydrochloric acid (50 c.c.) at 0°. After 3 hours the yellow crystalline stibinic chloride was collected, washed with hydrochloric acid, and hydrolysed by water to the stibinic acid, which was washed with water to remove occluded salts and finally dried in a vacuum desiccator. m-*Carbamidophenylstibinic acid*, a white amorphous powder, decomposed on heating, without melting * (Found: N, 9·5. $C_7H_7O_3N_2Sb,H_2O$ requires N, 9·1%).

The *sodium* salt, precipitated on adding alcohol to its neutral solution, formed a white amorphous powder, moderately easily soluble in water (Found: Sb, 39·0. $C_7H_8O_4N_2NaSb$ requires Sb, 37·0%). Most of the sodium salts gave high analytical figures for antimony. This accords with the observations of Fargher and Gray (*J. Pharm. Exp. Ther.*, 1921—1922, **18**, 341), who cite several instances of neutral sodium aryl stibinates containing less than one atom of sodium per molecule.

N-*Phenylglycineamide*-m-*stibinic Acid* (II).—A solution of *m*-aminophenylstibinic acid (5·2 g.) and chloroacetamide (3·6 g.) in *N*-sodium hydroxide (20 c.c.) was heated at 90° for 1½ hours. Sufficient sodium hydroxide was added to dissolve the resulting resinous precipitate and the solution, which still gave a reaction for primary aromatic amine, was treated with a further 1·5 g. of chloroacetamide and heated for another hour to complete the condensation. The clear solution obtained by adding the requisite amount of alkali was acidified with acetic acid, the precipitated stibinic acid was dissolved in 2*N*-hydrochloric acid (15 c.c.), and addition of ice-cold hydrochloric acid (*d* 1·19; 15 c.c.) then resulted in separation of the crystalline stibinic chloride. This chloride was rapidly collected and dissolved in water, the solution made alkaline, and the free stibinic acid reprecipitated by acetic acid (Found: Sb, 39·5; N, 9·0. $C_8H_9O_3N_2Sb,1/3H_2O$† requires Sb, 39·4; N, 9·1%). N-*Phenylglycineamide*-m-*stibinic acid*, a white amorphous powder, was readily soluble in dilute alkali or excess of dilute mineral acids but insoluble

* None of the stibinic acids described in the sequel had a definite melting point.

† Schmidt (*loc. cit.*) has shown that the vacuum-dried aryl stibinic acids are usually represented by formulæ of the type $3ArSbO_2,H_2O$ or $3ArSbO_2,2H_2O$. The figures for antimony which we have obtained have led us to adopt similar formulations, although with considerable reserve on account of the instability and difficulty of purification of the compounds.

in dilute acetic acid. When added to its dilute hydrochloric acid solution, sodium nitrite precipitated a gelatinous nitrosoamine.

The *sodium* salt, precipitated by addition of alcohol to its concentrated neutral aqueous solution, was a white amorphous powder readily soluble in water (Found: Sb, 35·9. $C_8H_{10}O_4N_2NaSb$ requires Sb, 35·5%).

Sodium N-*Phenylglycinemethylamide*-m-*stibinate* (III).—Condensation of *m*-aminophenylstibinic acid with chloroacetomethylamide was carried out exactly as with chloroacetamide, a double heating with the methylamide being also necessary for complete reaction. Phenylglycinemethylamide-*m*-stibinic acid, when purified through the stibinic chloride, had properties similar to those of the corresponding amide, and gave a strong odour of methylamine when heated with sodium hydroxide solution. The *sodium* salt, which was isolated from its concentrated aqueous solution by addition of alcohol and ether, formed a white amorphous powder completely soluble in about half its weight of water (Found: Sb, 33·1. $C_9H_{12}O_4N_2NaSb$ requires Sb, 34·1%).

Condensation of *m*-aminophenylstibinic acid with chloroacetethylamide proceeded smoothly with the formation of an acid, of which the sodium salt was not precipitated from its aqueous solution even by alcohol and ether.

pp′-*Diacetamidodiphenylstibinous Hydroxide.*—A suspension of *p*-acetamidophenylstibinous chloride hydrochloride (10 g.) in 0·005*N*-sodium hydroxide (1000 c.c.) was boiled for an hour. The solution, filtered hot from antimony oxide, deposited colourless needles on cooling; these, recrystallised from aqueous methyl alcohol, intumesced at 128° (Found: Sb, 29·5. Calc.: Sb, 29·9%). This process is simpler than Schmidt's method of degradation of the triacetamidotriphenylstibine (*Annalen*, 1922, **429**, 137).

This secondary hydroxide was oxidised to the diarylstibinic acid by Schmidt's method, and the product (4 g.) hydrolysed at 0° in ¾ hour by *N*-sodium hydroxide solution (25 c.c.). The resulting amino-compound gave only aniline and resinous products on treatment with chloroacetamide.

II. *Condensation of* 4-*Chloro*-3-*nitrophenylstibinic Acid with Amines.*

3-*Nitro*-4-*piperidinophenylstibinic Chloride Hydrochloride.*—A solution of 4-chloro-3-nitrophenylstibinic acid (3·28 g.) and piperidine (5·5 c.c.) in alcohol (20 c.c.) was boiled for 3 hours, and the solution poured into water. The orange precipitate (3·5 g.) was dissolved in warm glacial acetic acid (20 c.c.), and the cooled solution treated with concentrated hydrochloric acid (20 c.c.). The crystalline

precipitate was washed with a mixture of hydrochloric acid and acetic acid (1 : 1) and dried over sulphuric acid and solid potassium hydroxide. The *stibinic chloride hydrochloride* formed a colourless microcrystalline powder, decomp. 185—187° (Found : Sb, 24·3. $C_{11}H_{13}O_2N_2Cl_4Sb,HCl$ requires Sb, 24·1%).

3-*Nitro*-4-*piperidinophenylstibinic acid hydrochloride*, formed when the foregoing stibinic chloride was suspended in a large volume of water for several hours, was an orange amorphous powder (Found : Sb, 29·3. $C_{11}H_{13}O_4N_2Sb,H_2O,HCl$ requires Sb, 29·4%).

3-*Nitro*-4-*piperidinophenylstibinic Acid*.—The hydrochloride of the acid was dissolved in alcohol with 2*N*-sodium hydroxide; the clear solution was acidified with acetic acid. After drying, the gelatinous precipitate was again washed with water to remove occluded salts and obtained as an orange amorphous powder, sparingly soluble in excess of dilute aqueous alkali (Found : Sb, 33·6. $C_{11}H_{13}O_4N_2Sb,1/3H_2O$ requires Sb, 33·3%).

3-*Amino*-4-*piperidinophenylstibinic Acid* (VI).—Reduction of the nitro-compound with stannous chloride yielded no crystalline product, but the aminophenylstibinic acid was readily formed when ferrous hydroxide was used. A solution of 3-nitro-4-piperidinophenylstibinic acid (3 g.) in alcohol (15 c.c.) and 6*N*-sodium hydroxide (3 c.c.) was poured into water (150 c.c.), this procedure being adopted in order to obtain the substance in a finely divided state. More 6*N*-sodium hydroxide (30 c.c.) was added to the suspension, followed slowly by a solution of ferrous sulphate (15 g. in 100 c.c. of water). After 1½ hours the hydroxides of iron were removed and the filtrate was acidified with acetic acid. The gelatinous stibinic acid was purified through the stibinic chloride (obtained with ice-cold hydrochloric acid) (Found : Sb, 36·5. $C_{11}H_{15}O_2N_2Sb,1/3H_2O$ requires Sb, 36·3%).

3-*Amino*-4-*piperidinophenylstibinic acid* formed a greyish powder, soluble in very dilute mineral acid or alkali, the solutions giving reactions for primary amine. The *sodium* salt was produced when a suspension of the acid (3 g.) in 50% alcohol (80 c.c.) was neutralised with sodium hydroxide, the filtered solution evaporated to dryness, the residue extracted with boiling methyl alcohol, and the extract evaporated to dryness. This salt was too sparingly soluble in water to be used for intravenous injection (Found : Sb, 33·9. $C_{11}H_{16}O_3N_2NaSb$ requires Sb, 33·0%).

3-*Nitro*-4-*ethylaminophenylstibinic Chloride*.—A solution of 4-chloro-3-nitrophenylstibinic acid (3·28 g.) in alcoholic ethylamine (12 c.c. of a solution containing 22 g. of ethylamine per 100 c.c.) was heated at 120—130° for 3 hours. After cooling, an orange solid had separated consisting of the nitroethylaminophenylstibinic acid

mixed with antimony oxide. This crude product (1 g.) was ground under concentrated hydrochloric acid (20 c.c.) and the crystals were washed with concentrated hydrochloric acid and dried over sulphuric acid and solid potassium hydroxide. 3-*Nitro*-4-*ethylaminophenylstibinic chloride* formed a buff microcrystalline powder with no definite m. p. (Found: Sb, 28·6. $C_8H_9O_2N_2Cl_4Sb$ requires Sb, 28·4%). This stibinic chloride was immediately hydrolysed by water to the orange 3-*nitro*-4-*ethylaminophenylstibinic acid*, obtained pure for analysis by acidifying a dilute solution of the ammonium salt with acetic acid (Found: Sb, 37·1. $C_8H_9O_4N_2Sb,1/3H_2O$ requires Sb, 37·4%).

3-*Nitro*-4-*methylaminophenylstibinic chloride* was obtained in precisely the same manner as the ethylamino-compound from 4-chloro-3-nitrophenylstibinic acid (3·28 g.) and 15% alcoholic methylamine (15 c.c.) at 120—130° (Found: Sb, 28·8. $C_7H_7O_2N_2Cl_4Sb$ requires Sb, 29·3%).

III. *Acetylation of* 3-*Amino*-4-*hydroxyphenylstibinic Acid.*

The potassium salt (16 g.) of 3-nitro-4-hydroxyphenylstibinic acid (Schmidt, *Annalen*, 1920, **421**, 212) was reduced by sodium hydrosulphite (D.R.-P. 270,488) to the amino-compound, which was suspended in water (12 c.c.) and acetylated by the gradual addition of acetic anhydride (9 c.c.). This treatment led to a clear solution and after 24 hours several volumes of acetone were added to precipitate the *stibinic acid* (VII or VIII). The substance formed a white amorphous powder extremely soluble in water with an acid reaction, insoluble in acetone, alcohol or glacial acetic acid, and yielding a sodium salt readily soluble in water (Found: Sb, 37·8. $C_8H_8O_4NSb,H_2O$ requires Sb, 37·8%).

IV. *Quinolylstibinic Acids.*

The appropriate aminoquinoline (6 g.; 1/24 g.-mol.) in water (50 c.c.) and concentrated hydrochloric acid (20 c.c.) was diazotised at 0° with sodium nitrite (3 g.). The diazo-solution was added slowly, with simultaneous addition of 6*N*-sodium hydroxide (20 c.c.), to an ice-cold sodium antimonite solution prepared from antimony trichloride (12·6 g.), 5*N*-hydrochloric acid (20 c.c.), and glycerol (20 c.c.), the resulting solution being treated with 6*N*-sodium hydroxide until the precipitate first formed had just redissolved and then diluted to 800 c.c. After being kept at the ordinary temperature over-night, the solution was freed by filtration from the bulk of coloured by-products, and the filtrate acidified with acetic acid. The precipitate was suspended in concentrated hydrochloric acid (50 c.c.) and the product was collected after an hour and washed

with concentrated hydrochloric acid. The stibinic chloride, thus obtained free from antimony oxide, was decomposed by excess of dilute alkali, the stibinic acid being precipitated by acetic acid.

Quinolyl-5-stibinic Acid.—The crude stibinic acid (2 g. from 6 g. of 5-aminoquinoline) was converted into stibinic chloride by addition of concentrated hydrochloric acid to its solution in dilute hydrochloric acid, and the *stibinic acid* regenerated in the usual way. A small sample (0·5 g.) was further purified for analysis by extraction with boiling methyl alcohol (200 c.c.). The filtrate was concentrated to small bulk, and the deposit washed with methyl alcohol and dried (Found : Sb, 40·6. $C_9H_6O_2NSb,H_2O$ requires Sb, 40·6%). This acid formed a buff powder very sparingly soluble in most media, although moderately easily soluble in glacial acetic acid and readily soluble in dilute acids or alkalis. The *sodium* salt was obtained by adding a slight excess of sodium hydroxide to an aqueous suspension of the free acid (2·5 g.). The excess of alkali was neutralised with hydrochloric acid, and the filtrate evaporated to dryness in a vacuum desiccator. The residue was extracted with alcohol (30 c.c.), the solution filtered to remove sodium chloride, and then evaporated to dryness. This sodium salt was readily soluble in water (Found : Sb, 39·6. $C_9H_7O_3NNaSb$ requires Sb, 37·8%).

Quinolyl-5-stibinic chloride hydrochloride, obtained when a solution of the purified stibinic acid in dilute hydrochloric acid was treated at 0° with concentrated hydrochloric acid, was a buff microcrystalline powder, m. p. 222° (Found : Sb, 28·2. $C_9H_7NCl_5Sb$ requires Sb, 28·4%).

Quinolyl-6-stibinic Acid.—The crude stibinic acid (2 g. from 6 g. of 6-aminoquinoline) was purified through the stibinic chloride, and its filtered solution in methyl alcohol evaporated to dryness. The residual *acid* formed a buff powder moderately easily soluble in methyl alcohol and readily soluble in dilute acids or alkalis (Found : Sb, 40·1. $C_9H_6O_2NSb,H_2O$ requires Sb, 40·6%). The *sodium* salt, prepared and purified in the same manner as sodium quinolyl-5-stibinate, formed a straw-yellow powder readily soluble in water or alcohol (Found : Sb, 38·8. $C_9H_7O_3NNaSb$ requires Sb, 37·8%).

Quinolyl-6-stibinic chloride hydrochloride was obtained, by the addition of concentrated hydrochloric acid to an ice-cold solution of the stibinic acid in dilute hydrochloric acid, as a buff microcrystalline powder, m. p. 237° (Found : Sb, 28·5. $C_9H_7NCl_5Sb$ requires Sb, 28·4%).

Quinolyl-8-stibinic Acid (IX).—(a) *Water-insoluble form.* The crude acid (3·6 g. from 6 g. of 8-aminoquinoline) was purified in the same way as the 6-stibinic acid and formed a light brown powder moderately easily soluble in methyl alcohol, readily soluble in dilute

acids, but soluble only in excess of sodium hydroxide (Found : Sb, 41·3. $C_9H_6O_2NSb,2/3H_2O$ requires Sb, 41·4%).

(b) *Water-soluble form.* Purified quinolyl-8-stibinic acid (3 g.) was dissolved in 0·2*N*-acetic acid (50 c.c.), and the solution evaporated to dryness. The residue was redissolved in water, and the solution again evaporated to dryness in a vacuum desiccator. The resulting light brown powder was readily soluble in water, addition of a drop of sodium hydroxide resulting in precipitation of the insoluble form (Found : Sb, 40·2. $C_9H_6O_2NSb,H_2O$ requires Sb, 40·6%).

Quinolyl-8-stibinic chloride hydrochloride (X) separated, when concentrated hydrochloric acid was added to an ice-cold methyl-alcoholic solution of the stibinic acid, in small brownish needles, decomp. 200—210° (Found : Sb, 28·4. $C_9H_7NCl_5Sb$ requires Sb, 28·4%).

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