ARYL DI- & POLY-STIBINIC ACIDS, DISTIBINOUS OXIDES AND DISTIBINO-COMPOUNDS.*

By Sohrab M. Mistry and Praphulla Chandra Guha.

The importance of organic antimonials as trypanocides was discovered when Plimmer and Thomsen (*Proc. Roy. Soc.*, 1908, B **80**. 1) found that trypanosomes rapidly disappeared from the blood of infected animals on injection with antimony compounds. The importance of the stibinic acids as trypanocides has stimulated research from the standpoint of chemotherapy. From the little work that has been done, very few conclusions could be drawn as regards the relationship between chemical constitution and therapeutic properties of organo-antimony compounds. The stibinic acid grouping $-SbO(OH)_2$ has the characteristic trypanocide property, but it is believed that this is due to the formation *in vivo* of trivalent $-Sb=O$ as the real trypanocide (*cf.* Brahmachari, *Ind. Sci. Congress. Med. Sec.*, 1931). It is an established fact, however, that the substituents in the nucleus of an aromatic stibinic acid also exert a marked influence. Thus the introduction of an amino-group in the aryl nucleus of a stibinic acid diminishes toxicity to a considerable extent, and acetylation of the amino-group increases the diminution. The acetylated product, however, being more unstable becomes toxic on keeping and hence useless as a therapeutic agent (Brahmachari, *Ind. J. Med. Res.*, 1922, **10**, 521 ; also *loc. cit.*). In the arsenic series the acetylation of an amino-group renders the compound more active. Stibinic acids substituted both by chloro- and amino-groups are also active anti-kala-azar remedies. Again, stibinic acids derived from aminobenzylbenzoates and benzylaminobenzoate have been found to be without any marked curative action on kala-azar (Niyogy, *J. Ind. Chem. Soc.*, 1930, **7**. 577).

Although the discovery of the most important synthesis of stibinic acids by the diazo-reaction (first applied by Bart, 1910, to the synthesis of arsonic acids) is attributed to the Chemische Fabrik von Heyden (1912, *D. R. P.*, 254,421), P. May was the first to publish a paper (*J. C. S.*, 1912, **101**. 1032) describing a few double salts of antimony trichloride and aryl diazochlorides. The alkali treatment of these double salts would have given him the corresponding stibinic acids ; but this was first mentioned in a German patent (*D. R. P.*, 261,825). A thorough discussion of the reactions involving the formation of a stibinic acid by the diazo-reaction is due to H. Schmidt (*Annalen*, 1920, **421**, 174 ; **429**, 123 ; *Ber.*, **55B**, 697 ; *ibid.*, **57B**. 1142 ; *ibid.*, **59**, 555).

Urea stibamine discovered by Brahmachari (*Ind. J. Med. Res.*, 1922, **10**, 508 ; 1924, **12**, 423) to which the structure $NH_2.CO.NH.C_6H_4.SbO(OH)(ONH_4)$-*p* was originally attributed, has had phenomenal success in the cure of kala-azar. It has now been found that it is not an individual, but most probably a mixture (*J. Soc. Chem. Ind.*, 1930, **49**, 800). Niyogy on the other hand (*J. Ind. Chem. Soc.*, 1928, **5**, 757), however, claims to have obtained a

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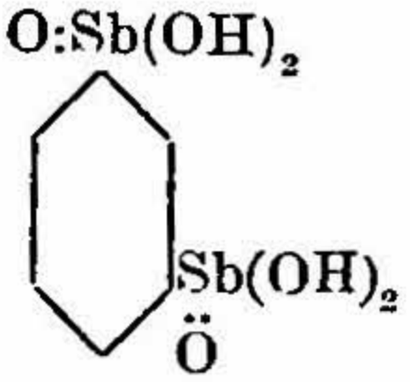
* Preliminary reports on this work have been published in the *Proceedings of the Indian Science Congress* (Chemistry Section, 1930, 176 ; 1931, 162), and have been communicated before the preceding 15th October of each year.

product by treating a hydrochloric acid solution of *p*-aminophenylstibinic acid with potassium cyanate which he considers to be identical with urea stibamine.

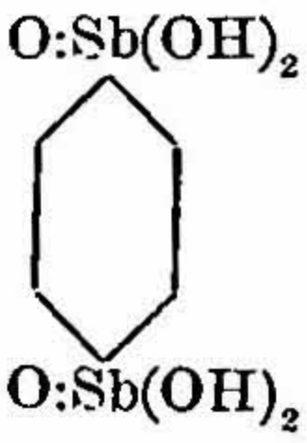
The present investigation was undertaken to prepare a series of compounds the pharmacological examination of which was likely to throw some further light on the chemotherapy of organic antimonials. If the stibinic acid grouping had any influence on the trypanocidal property it was thought worth while to investigate various types of aromatic compounds having more than one stibinic acid group in the molecule. The compounds prepared can be divided into five categories :—(*a*) where antimony is attached to one and the same aryl nucleus ; (*b*) where antimony is attached to different aryl nuclei directly connected ; (*c*) the same as (*b*) but with the aryl nuclei connected through one or more carbon atoms ; (*d*) two antimony-containing aryl groups connected through carbon and nitrogen atoms, and (*e*) antimony-containing aryl groups linked through nitrogen, phosphorus, arsenic or antimony.

Although mixed arsono-stibinic acids had been prepared by several workers in this field (*D. R. P.*, 296,940 ; Schmidt, *Ber.*, 1924, **57B**, 1147), no distibinic acid appeared to have been known when this work was undertaken. Dunning and Reid (*J. Amer. Chem. Soc.*, 1926, **48**, 2959) claimed to have obtained diphenyldistibinic acid from benzidine by tetrazotisation and subsequent stibination, but they did not give details of their method, while the percentage of antimony in the compound was 4 per cent. above the theoretical value. During the progress of this work, however, Riddel and Basterfield's paper (*Proc. Roy. Soc. Canada*, 1930, **23**, I (III), 45) came to our notice where they reported failure to obtain a distibinic acid from benzidine and described the preparation of distibinic acids from *pp'*-diaminodiphenylmethane and *p*-phenylenediamine.

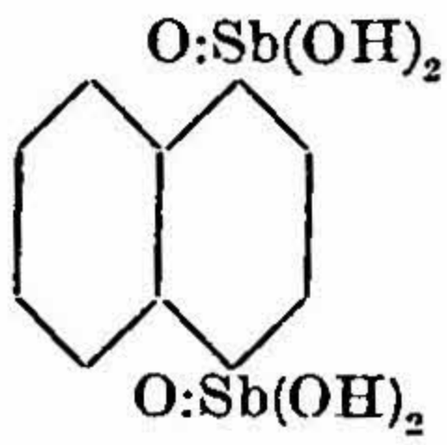
m-Phenylenediamine, *p*-phenylenediamine and 1 : 4-naphthylenediamine have now been found to give the corresponding distibinic acids (I-III) :



(I)



(II)

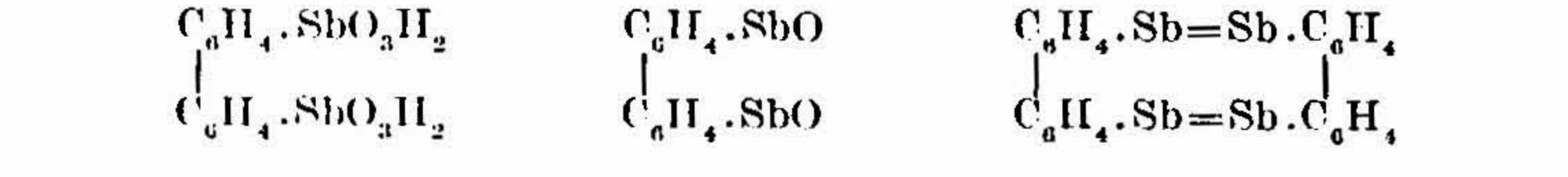


(III)

On repeating Dunning and Reid's work, it was found that the double compound of tetrazotised benzidine and antimony trichloride (*cf.* May, *J. C. S.*, 1912, **101**, 1037), on treatment with alkali gave an orange-brown, amorphous mass, the insolubility in alkali proving the absence of a stibinic acid group. Moreover, the compound was soluble in glacial acetic acid from which it could be precipitated by water as a light yellow powder ; it did not dissolve in concentrated hydrochloric acid but became deep violet, the colour disappearing on dilution with water, showing that the insoluble chloride is hydrolysed at lower concentration of the acid. Further, it was found that while alkaline hydrogen peroxide had no effect on this compound it is decomposed by more drastic oxidising agents. The above properties and the results of analysis support the distibinous oxide structure, $C_{12}H_8(SbO)_2$. Sodium thiosulphate reduces the

compound to a red powder which is completely decomposed without colouration by concentrated hydrochloric acid.

This is the first instance in which a trivalent antimonial has been obtained in a reaction which usually gives stibinic acids. Although the mechanism by which the distibinous oxide is formed is not quite clear, we suggest that most probably the distibinic acid is formed first by analogy with the Bart-Schmidt reaction and becomes easily reduced to the stable distibinous oxide, thus :—



(IV) (IV *a*)

There being so much controversy on the structure of diphenyl and its derivatives, nothing can be said with certainty as to whether the space relation between the two stibinic acid groups in the *para*-positions of diphenyl is responsible for this anomalous behaviour. For comparison the diarsenic acid from benzidine was prepared and a good yield of the acid obtained.

Compounds (V and VI) similar to that obtained from benzidine were obtained from *o*-tolidine and dianisidine :—

(V) (VI)

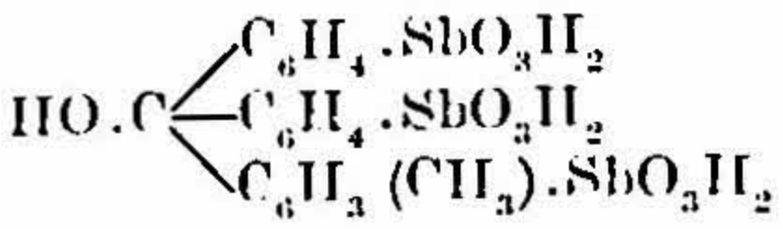
Riddel and Basterfield (*loc. cit.*) claim to have isolated a distibinic acid from *pp*-diaminodiphenylmethane though they failed to purify their product; our independent experiments before the paper came to our notice disagree with those of the above authors since we could isolate only a distibinous oxide (VII) and no stibinic acid. Our repeated experiments have only confirmed the above disagreement, but *pp*-diaminobenzophenone does give the corresponding distibinic acid (VIII).

(VII) (VIII)

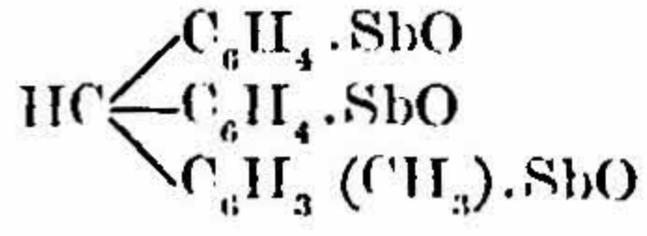
In the case of *pp*-diaminodiphenylmethane the distibinic acid is most probably formed, but reduction leads to the stable stibinous oxide form. In this connection it is interesting to note that the amino-groups of *pp*-diaminodiphenylmethane react easily with camphorquinone but those of *pp*-diaminobenzophenone do not (unpublished work). The influence of the methylene group in rendering the substituent stibinic acid grouping liable to reduction, in contradistinction to the stabilising effect produced by the carbonyl group, has been observed

in the antimony compounds obtained from *pp*-diaminodiphenylurea, *pp*-diaminodiphenylmethylenediamine, *pp*-diaminodiphenyloxamide and *pp*-diaminodiphenylethylenediamine (XIII, XIV, XVII and XV).

On being subjected to the Bart-Schmidt method of stibination, rosaniline yielded the expected tristibinic acid (IX) but leucaniline gave only a tristibinous oxide (X) to the complete exclusion of the expected stibinic acid.



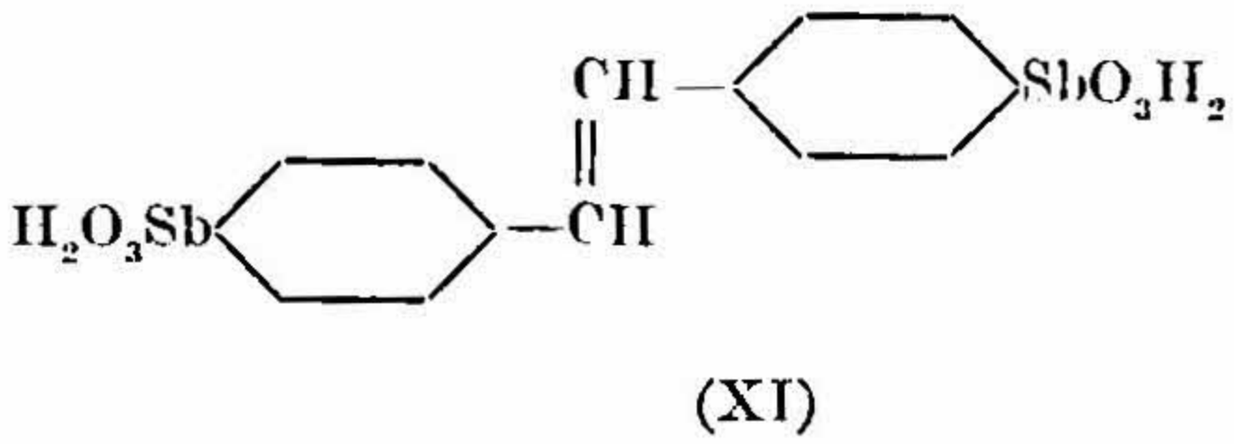
(IX)



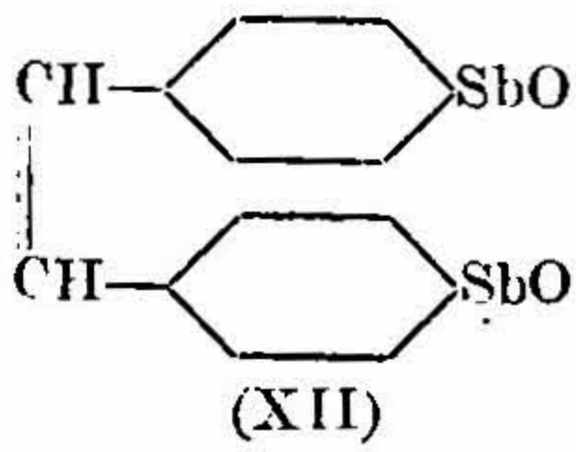
(X)

Reduction of the carbinol is evidently accompanied by a great change in property similar to that observed in the formation of compounds VII and VIII from diaminodiphenylmethane and diaminobenzophenone.

A distibinic acid (XI) and a distibinous oxide (XII) have been isolated from the product of stibinating *pp*-diaminostilbene. Formation of these different products may be explained by assuming that the *cis*-form of the diamine gives the distibinous oxide and the *trans*-form the distibinic acid. In the *cis*-form the two *para*-positions of the phenyl nuclei being so close together cannot retain two heavy acidic groups, whereas the *para*-positions of the *trans*-form being further apart can easily accommodate the stibinic acid groups :—



(XI)



(XII)

Compounds were next prepared in which the two stibinic acid groups were attached to two different aromatic nuclei separated from each other by a link of carbon and nitrogen atoms in varying number. The first compound of this series was prepared from *sym*-*pp*-diaminodiphenylurea, selected because the expected distibinic acid would be Brahmachari's supposed *p*-carbaminophenylstibinic acid with one more phenylstibinic acid grouping attached to the carbamido-group, and should possess trypanocidal properties in a much more pronounced degree. The double compound obtained by tetrazotisation and coupling with antimony trichloride on analysis agreed with the formula,

and on treatment with alkali gave a sparingly soluble brown powder which became deep violet on treatment with concentrated hydrochloric acid, regaining its original colour on dilution. Analysis proved the presence of only one

atom of antimony in the molecule, however, and the formula corresponded to that of a monostibinic acid. To explain this peculiar reaction, *p*-monoaminodiphenylurea was stibinated by the usual method and a compound agreeing in all its properties with the stibinic acid prepared from *sym-pp*-diaminodiphenylurea was obtained. As is well known, it is extremely difficult to purify stibinic acids, and it is impracticable to prove the identity of stibinic acids obtained from two different sources; conclusions must be drawn from solubility and other physical properties in conjunction with results of analysis.

The mechanism of the reaction can be explained as follows: During alkali treatment of the double salt one of the $N_2Cl,SbCl_3$ groups is transformed as usual into a stibinic acid group while the other is replaced by an atom of hydrogen:

$$OC\begin{cases}NH.C_6H_4.N_2Cl,SbCl_3\\NH.C_6H_4.N_2Cl,SbCl_3\end{cases}\qquad OC\begin{cases}NH.C_6H_4.SbO(OH)_2\\NH.C_6H_4.N_2Cl,SbCl_2\end{cases}$$

$$OC\begin{cases}NH.C_6H_4.SbO(OH)_2\\NH.C_6H_5\end{cases}$$

The replacement of a diazo-complex by hydrogen is of common occurrence in such reactions and is not at all unexpected (*cf.* Christiansen, "Organic Derivatives of Antimony", p. 57).

A primary stibinic acid of this type would be readily soluble in alkali, but as has been mentioned above the product is sparingly soluble in sodium hydroxide solution. This fact could be better explained on the ground that a secondary stibinic acid is formed by the elimination of a molecule of water from the hydroxyl group of the phenyl-carbamino-4-phenylstibinic acid and the *para*-hydrogen atom of the other phenyl group, thus:—

$$OC\begin{cases}NH.C_6H_4.SbO(OH)_2\\NH.C_6H_5\end{cases}\qquad OC\begin{cases}NH.C_6H_4\\NH.C_6H_4\end{cases}SbO.OH$$

(XIII)

Macallum (*J. Soc. Chem. Ind.*, 1923, 468 T) describes an analogous condensation and claims to have obtained a secondary stibinic acid as the main product of action between antimony trioxide and *o*-chlorobenzenediazonium chloride.

pp-Diaminodiphenylmethylene- and ethylenediamines gave distibinous oxides (XIV) and (XV) instead of the stibinic acids obtained from *pp*-aminodiphenylurea and oxamide

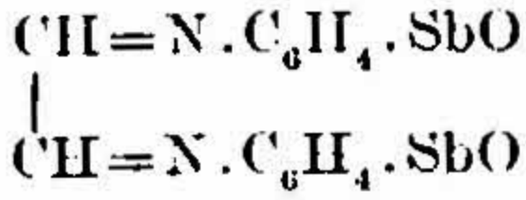
$$CH_2\begin{cases}NH.C_6H_4.SbO\\NH.C_6H_4.SbO\end{cases}\qquad \begin{matrix}CH_2.NH.C_6H_4.SbO\\|\\CH_2.NH.C_6H_4.SbO\end{matrix}$$

(XIV) (XV)

The formation of these two stibinous oxides is evidently due to the methylene and ethylene groups, the directing influence of which in the formation of

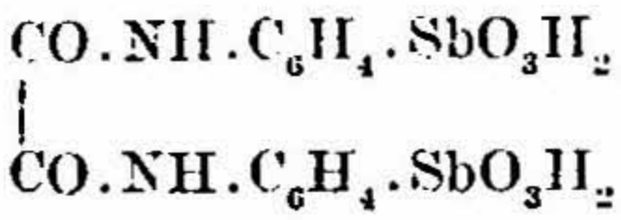
stibinous oxides in preference to stibinic acids having already been shown (*cf.* VII-X).

Bis-acetylaminophenylazomethine was obtained by treating two molecules of acetyl-*p*-phenylenediamine with one molecule of glyoxal, and on hydrolysis gave the corresponding diamine from which on stibination the distibinous oxide (XVI) was obtained :

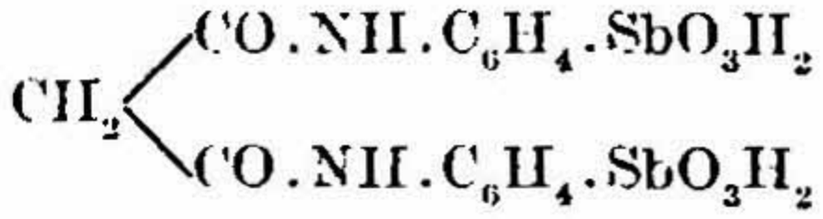


(XVI)

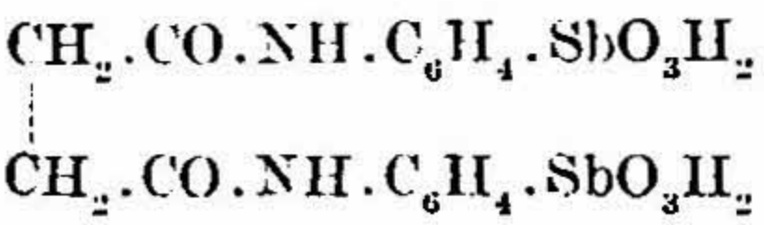
pp-Diaminodiphenyloxamide, -malonamide, -succinamide and -carbohydrazide yielded the distibinic acids (XVII-XX) :



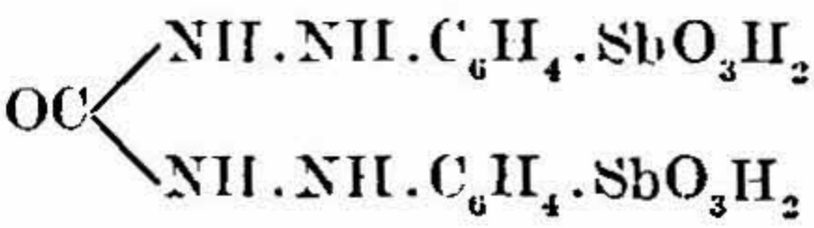
(XVII)



(XVIII)

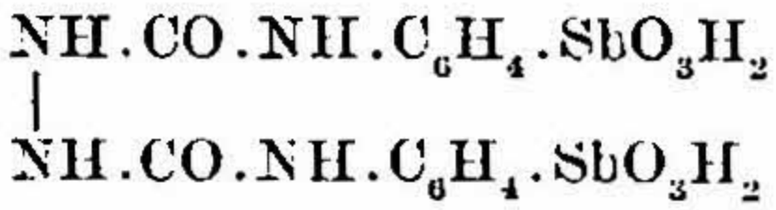


(XIX)



(XX)

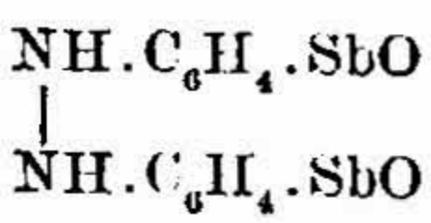
pp-Diaminodiphenylhydrazodicarbonamide, prepared for the first time, gave a distibinic acid on stibination in the usual manner :—



(XXI)

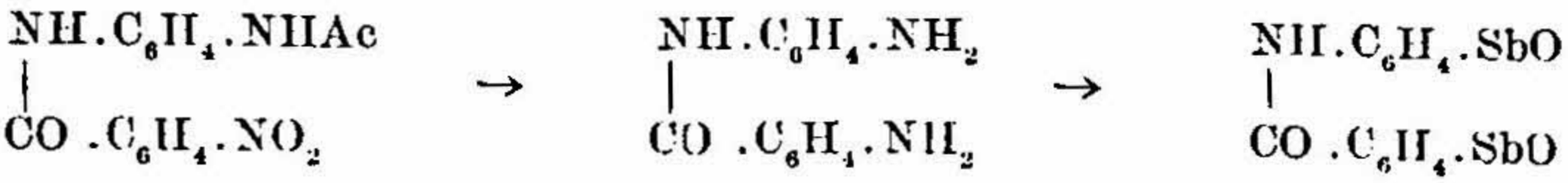
It will be seen that this is really a *bis*-compound of Brahmachari's urea stibamine, and as such is very likely to be a valuable trypanocide.

pp-Diaminohydrazobenzene on stibination gave a distibinous oxide :—



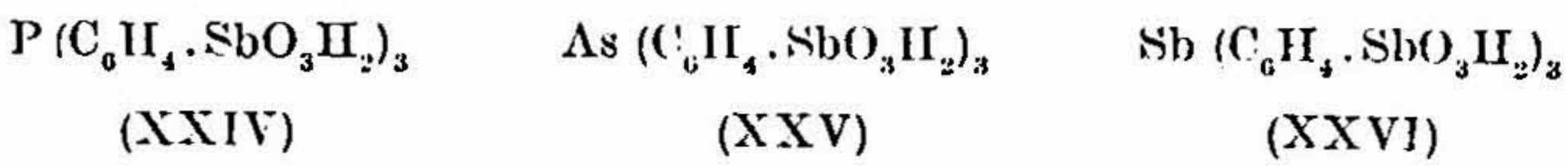
(XXII)

pp-Diaminobenzanilide has been prepared for the first time by the interaction of *p*-nitrobenzoyl chloride and acetyl–*p*-phenylenediamine, followed by reduction and hydrolysis. It gave on stibination the distibinous oxide (XXIII) :—



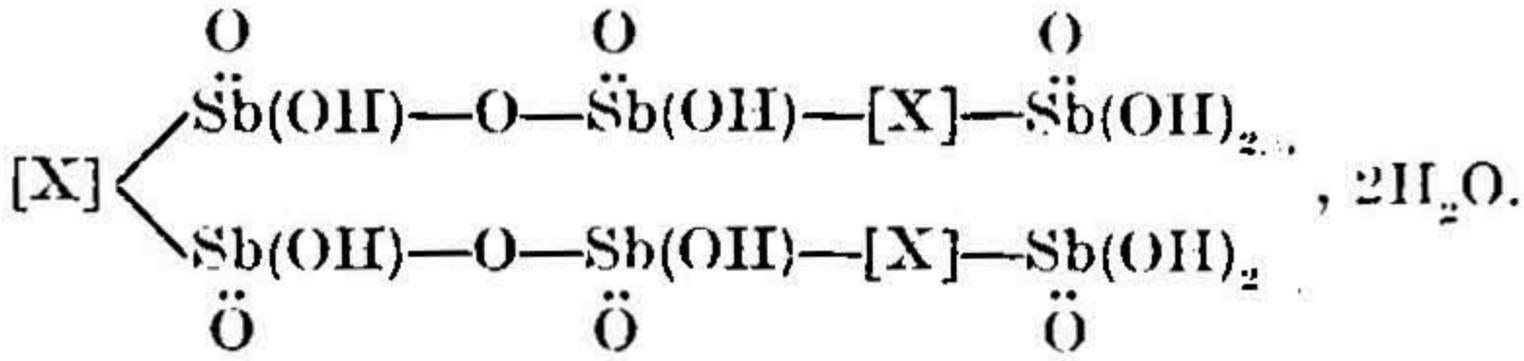
(XXIII)

To study the effect of phosphorus, arsenic and antimony in *mmm*-triaminotriphenylphosphine, -arsine and -stibine respectively on stibination they have been subjected to the Bart-Schmidt method of stibination with the result that all of them have been found to yield the corresponding tristibinic acids (XXIV–XXVI). The combination of the three stibinic acid groups with other atoms of phosphorus, arsenic and antimony is likely to impart interesting pharmacological properties to these compounds. The triphenylphosphine, -arsine, and -stibine were prepared by a slightly modified method of Pfeiffer and his co-workers (*Ber.*, 1904, **37**, 4621). and the yields were considerably improved.



(XXIV) (XXV) (XXVI)

In all cases the simple formula for the distibinic acids is given for the sake of saving space. According to Schmidt's complex formula for the stibinic acids they should be represented by a general formula of the type :



[X] representing the bivalent organic part of the molecule.

Experimental.

Of all the known methods for the preparation of stibinic acids by the diazo-reaction, the method of the *D.R.P.* 261,825 has been found to be the best. The amine is fully diazotised, a solution of antimony trichloride is added, the crystalline double salt is filtered and freed from inorganic antimony as much as possible by washing with dilute hydrochloric acid. The compound thus purified is treated with excess of 5*N* sodium hydroxide solution and vigorously stirred with cooling to ensure the maximum yield.

Various methods of purifying the stibinic acids are known but most of them are either wasteful or unsuitable. After many trials, the following method has been adopted for purification of the stibinic acids described in this paper. The crude acid is dissolved in very dilute sodium hydroxide solution and precipitated by very dilute hydrochloric acid ; this is repeated several times. the acid being allowed to settle and separated by decantation. Coagulation of the colloidal acids is easily effected by saturating the solution with common salt. Finally, the acid is filtered, washed thoroughly with water and the adsorbed inorganic matter removed by shaking repeatedly with a large quantity of water for three or four days.

When the double compound of the aryl-diazoniumchloride and antimony trichloride gives with alkali an insoluble product, this is filtered and washed with water and extracted thoroughly with a large quantity of glacial acetic acid ; warming the mixture is not harmful as decomposition is very slight below 60°. The extract is poured drop by drop into a large quantity of very dilute ammonia, when an amorphous precipitate is formed and is further purified by repeating the process. Thorough washing with ether gives finally a pure sample of the distibinous oxide.

Two of the best methods available for the estimation of antimony are those of Ghosh (*Ind. J. Med. Res.*, 1928, **16**, 458) and Macallum (*J. Soc. Chem. Ind.*, 1923, **42**, 470). Ghosh's method is the safer, although tedious, and the results agree very well. In a few cases, confirmatory estimations were carried out by Macallum's method and the results found to be quite satisfactory, care being always taken to decompose the organic matter very slowly.

m-*Phenylenedistibinic acid* (I).—A mixture of *m*-phenylenediamine hydrochloride (10 g.) and antimony chloride (28 g.) was diazotised and the dark red double salt treated with alkali. A dark red solution was obtained when evolution of nitrogen ceased, and on acidification gave a dark brown, colloidal precipitate which was purified in the usual manner (yield, 5 g.). The acid is insoluble in hydrochloric acid but is easily soluble in alkalis (Found : Sb, 57.7 ; $C_6H_8O_6Sb_2$ requires Sb, 58.1 per cent.).

p-*Phenylenedistibinic acid* (II).—The double salt was dark grey and darkened on exposure to air (Found : Sb, 57.8 ; $C_6H_8O_6Sb_2$ requires Sb, 58.1 per cent.).

1 : 4-*Naphthylenedistibinic acid* (III).—1 : 4-Naphthylenediamine sulphate was prepared by the method of Griess (*Annalen*, 1866, **137**, 60). A solution of the diamine sulphate (5 g.) and antimony trioxide (8 g.) in hydrochloric acid (50 c.c.) was carefully diazotised and the resulting yellow double compound treated with 5*N* sodium hydroxide solution. The greenish brown distibinic acid obtained on acidification (yield, 0.5 g.) was purified in the usual manner (Found : Sb, 50.8 ; $C_{10}H_{10}O_6Sb_2$ requires Sb, 51.9 per cent.).

Diphenylene-pp-*distibinous oxide* (IV).—A mixture of benzidine (20 g.) and a solution of antimony trioxide (30 g.) in concentrated hydrochloric acid was diazotised with sodium nitrite (10 g.). The double salt was soluble in concentrated hydrochloric acid from which it was precipitated by water as a bright yellow, crystalline powder ; alkali treatment gave an insoluble orange-brown product which on extraction became a light yellow powder (5 g.). Concentrated hydrochloric acid produces an intense violet colouration which disappears on dilution with water (Found : Ghosh ; Sb, 57.9, 57.5, 57.3, 57.8, 56.9 : Macallum ; Sb, 58.1, 57.3 ; mean 57.54 ; C, 29.95 ; H, 1.91. $C_{12}H_8O_2Sb_2$ requires Sb, 56.96 ; C, 30.1 ; H, 2.09 per cent.).

pp-*Distibinotetraphenylene* (IV *a*).—A small quantity of the finely powdered diphenylene-*pp*-distibinous oxide was heated with aqueous sodium thiosulphate solution on the water bath for three hours when the colour changed to deep red ; the filtered product was washed with carbon bisulphide to remove traces of sulphur, but isolation of the pure distibino-compound was extremely difficult. Hydrochloric and glacial acetic acids decomposed it, the results of analysis being consequently variable.

3 : 3-*Dimethyldiphenylene*-4 : 4'-*distibinous oxide* (V).—A solution of *o*-tolidine (5 g.) and antimony trioxide (8 g.) in hydrochloric acid was tetrazotised, and the yellow double salt treated with 5*N* sodium hydroxide solution : after vigorous evolution of nitrogen a brown insoluble residue remained. Extraction with glacial acetic acid gave an orange powder (3 g.) which became a brilliant violet with hydrochloric acid (Found : Sb, 53.4 ; $C_{14}H_{12}O_2Sb_2$ requires Sb, 53.4 per cent.).

Distibinotetramethyltetraphenylene.—A small quantity of the distibinous oxide (V) was finely powdered and heated on the water bath with an aqueous solution of sodium thiosulphate for two hours, when the colour changed from orange to brilliant red. The substance was filtered, washed with water, alcohol and then with carbon disulphide to remove all traces of sulphur, but the substance was found on analysis to be impure. It is insoluble in all organic solvents and is decomposed by mineral acids, liberating inorganic antimony instead of becoming violet.

3 : 3'-*Dimethoxydiphenylene*-4 : 4'-*distibinous oxide* (VI), prepared from dianisidine in the usual manner was obtained after extraction with glacial acetic acid as an orange powder (2 g.), and gave a violet colouration with hydrochloric acid (Found : Sb, 49.5 ; $C_{14}H_{12}O_4Sb_2$ requires Sb, 49.9 per cent.).

Diphenylmethane-pp-*distibinous oxide* (VII).—*pp*-Diaminodiphenylmethane was prepared according to the method of Kauffer and Borel (*Ber.*, 1907, **40**, 3254), the 2 : 4- and 4 : 4-isomerides being separated by the method of King (*J.C.S.*, 1920, **117**, 988). The diamine was diazotised in presence of antimony trioxide dissolved in hydrochloric acid and the deep yellow double salt on alkali treatment gave a product insoluble in alkali. The glacial acetic acid extract was red, yielding the distibinous oxide as a light yellow powder (yield, about 5 per cent.). It dissolved in concentrated hydrochloric acid giving a red solution from which the distibinous oxide could be precipitated by ammonia (Found : Sb, 55.0 ; $C_{13}H_{10}O_2Sb_2$ requires Sb, 55.2 per cent.).

Benzophenone-pp-*distibinic acid* (VIII).—*pp*-Diaminobenzophenone was prepared from *pp*-diaminodiphenylmethane by the method of Rivier and Farine (*Helv. Chem. Acta*, 1929, **12**, 866). Stibinated as in the case of *pp*-diaminodiphenylmethane, the bright yellow double salt on treatment with alkali gave a scarlet solution which on acidification gave the brown distibinic acid (yield, about 50 per cent.). The free acid does not show any colouration with hydrochloric acid and is quite stable when dry (Found : Sb, 46.2 ; $C_{13}H_{12}O_7Sb_2$ requires Sb, 46.5 per cent.).

Diphenyl-m-*tolylmethylcarbinol*-ppp-*tristibinic acid* (IX).—Rosaniline (5 g.) was diazotised and combined with antimony trichloride, the orange double salt being treated with alkali under ice-cooling ; a red solution of the sodium salt was obtained from which the free tristibinic acid was precipitated as a brown colloidal mass (1.5 g.). The usual method of purification was employed (Found : Sb, 45.9 ; $C_{20}H_{21}O_{10}Sb_3$ requires Sb, 46.5 per cent.).

Diphenyl-m-*tolylmethane*-ppp-*tristibinous oxide* (X).—Leucaniline (2 g.) was mixed with the required quantity of antimony trichloride and diazotised. The orange double salt with alkali under ice-cooling gave a very poor yield of an insoluble amorphous brown residue which dissolved in glacial acetic acid

with a deep purple colouration, thus resembling diphenylmethane-*pp*-distibinous oxide (VII). The tristibinous oxide was a dark grey powder (Found : Sb, 55.0 ; $C_{20}H_{15}O_3Sb_3$ requires Sb, 54.6 per cent.).

Stilbene-4 : 4'-distibinic acid (XI) and *stilbene-4 : 4'-distibinous oxide* (XII).—*pp'*-Diaminostilbene was prepared from the *pp*-dinitro compound by reduction with tin and hydrochloric acid (Horman, *J. pr. Chem.*, 1889, ii, **39**, 502), the dinitro-compound having been prepared in its turn from *p*-nitrobenzyl chloride (*Ber.* 1876, **6**, 328 : 1890, **23**, 1959). The dinitro-compound melted at 281°, not at 280-285° as stated by previous workers, and *pp*-diaminostilbene melted at 226-227°.

Preparation of the antimony compounds.—The diamine (2 g.) was mixed with antimony trichloride dissolved in concentrated hydrochloric acid (30 c.c.) and diazotised. The bright yellow double salt purified in the usual manner was treated with 5*N* sodium hydroxide solution under ice-cooling. The brownish red filtrate gave on acidification a colloidal distibinic acid (0.2 g.) which did not develop the violet colouration (Found : Sb, 45.8 ; $C_{14}H_{14}O_6Sb_2$ requires Sb, 45.8 per cent.).

In this reaction, besides the brown filtrate a large quantity of an insoluble product was obtained and extracted with glacial acetic acid giving a pale brown distibinous oxide (0.4 g.) with ammonia (Found : Sb, 54.3 ; $C_{14}H_{10}O_2Sb_2$ requires Sb, 53.6 per cent.). The quantity of the distibinic acid was much less than that of the distibinous oxide and the conditions of experiment did not seem to have much effect on the yield of the distibinic acid. The diamino-compound used was the one described in literature (m.p. 226-227°) and no attempt was made to prepare the antimony compound by Schmidt's modification of Bart's method.

The double salt, $CO(NH.C_6H_4.N_2Cl,SbCl_2,HCl)_2$.—*sym-pp*-Diaminodiphenylurea was prepared by the improved method of Mistry and Guha (*J. Ind. Chem. Soc.*, 1930, **7**, 793). The diamine (4.5 g.) was diazotised and combined with antimony trichloride, the bright yellow double salt being washed repeatedly with dilute hydrochloric acid and with water, and then dried in a vacuum desiccator over calcium chloride (Found : Sb, 25.9 ; $C_{13}H_{12}ON_6Cl_{10}Sb_2$ requires Sb, 28.0 per cent.).

The secondary monostibinic acid (XIII).—The foregoing double salt was treated with alkali and when the evolution of nitrogen had ceased the reaction mixture was warmed on the water bath for a few minutes and then filtered. The residue was extracted repeatedly with warm dilute alkali until no more dissolved, the alkaline extract on acidification giving a brown colloidal product (1.0 g.), sparingly soluble in alkali and coloured deep violet by hydrochloric acid. Samples of different preparation were identical in appearance and gave concordant results of analysis (Found : Sb, 32.9 ; C, 42.4 ; H, 2.9 ; $C_{13}H_{11}O_3N_2Sb$ requires Sb, 33.3 ; C, 42.8 ; H, 3.0 per cent.).

The same *monostibinic acid* (XIII) from *p*-aminodiphenylurea.–The amine was prepared according to the method of Mistry and Guha (*loc. cit.*), and the method of preparing the antimony compound was the same as in the foregoing experiment (Found : Sb, 33.1 ; C, 42.4 ; H, 3.1). The product (0.5 g.) was identical in appearance and chemical behaviour with the antimony compound obtained from *pp*-diaminodiphenylurea.

4 : 4′-*Diacetylaminodiphenylmethylenediamine.*—Although known in the literature, no details are given for its preparation. A solution of acetyl-*p*-phenylenediamine (12 g.) and methylene bromide (3.5 g.) in amyl alcohol was heated under reflux for three hours. The solid formed on cooling was washed with water and boiled with alcohol; the grey, insoluble product (m.p. 220°, yield 2 g.) was hydrolysed by boiling with hydrochloric acid and the resulting solution on evaporation gave the desired dihydrochloride. The quantity of acetyl-*p*-phenylenediamine should always be in sufficient excess for absorbing the hydrochloric acid formed in this reaction as otherwise this might cause premature hydrolysis. The yield is very low but the method is convenient.

Methylenediaminophenylene–4 : 4′-*Distibinous oxide* (XIV).—Diaminodiphenylmethylenediamine hydrochloride (2 g.) was tetrazotised and combined with antimony trichloride, the bright yellow double salt being treated with alkali in the usual manner. The brown, alkali-insoluble residue in very poor yield, was purified by extraction with glacial acetic acid, when the pale brown powder gave a violet colouration with hydrochloric acid (Found: Sb, 51.2; $C_{13}H_{12}O_2N_2Sb_2$ requires Sb, 51.6 per cent.).

4 : 4′-*Diacetylaminodiphenylethylenediamine.*—This compound was prepared from ethylene dibromide (1 mol.) and acetyl-*p*-phenylenediamine (4 mol.), the purified product melting with decomposition at 284° (Found: N, 14.0; $C_{18}H_{22}O_2N_4$ requires N, 14.11 per cent.). The diacetyl compound on hydrolysis gave the hydrochloride which was used for stibination.

Ethylenediaminodiphenylene-pp-*distibinous oxide* (XV).—The deep yellow antimony chloride double salt produced an insoluble brown mass on alkali treatment; the glacial acetic acid extract gave when poured into ammonia, a very poor yield of the brownish distibinous oxide showing the violet colouration with hydrochloric acid (Found: Sb, 50.4; $C_{14}H_{14}O_2N_2Sb_2$ requires Sb, 50.2 per cent.).

Bis-p-*aminophenylazomethine.*—Glyoxal sodium bisulphite (5 g.) was warmed with 25 c.c. of water and 3 or 4 drops of sulphuric acid for four hours, a little more acid being added at the later stage of the decomposition, when a clear solution of the free glyoxal was obtained. This solution, together with the required quantity of an alcoholic solution of acetyl-*p*-phenylenediamine, was heated under reflux for an hour when crystals began to separate. The crystals were filtered, and the filtrate yielded two more crops on concentration, the assembled product crystallising from alcohol in silvery plates, m.p. 279° (decomp.). The free *base* was prepared by hydrolysing the diacetyl compound with aqueous-alcoholic hydrochloric acid on the water bath till the reaction mixture left no insoluble residue on being diluted with water. The solution on being treated with dilute ammonia deposited silvery crystals of the free diamine m.p. 258° (decomp.) (Found: N, 17.31; $C_{18}H_{18}O_2N_4$ requires N, 17.28 per cent.).

Bis-phenylazomethine-pp′-*distibinous oxide* (XVI).—The free base (2 g.) mixed with antimony trichloride and hydrochloric acid was diazotised, the orange yellow double salt on being treated with alkali under ice-cooling giving a very poor yield of a reddish brown powder which on extraction with glacial acetic acid became a dirty red (Found: Sb, 49.1; $C_{14}H_{10}O_2N_2Sb_2$ requires Sb, 50.57 per cent.).

sym-*Oxalaminodiphenylene*-pp-*distibinic acid* (XVII).—*sym-pp*-Diaminodiphenyloxamide was prepared according to the method of Mistry and Guha (*loc. cit.*). The orange coloured double salt obtained from the diamine by diazotisation and combination with antimony trichloride was treated with alkali under ice-cooling and stirring, the solution giving on acidification an orange-grey colloidal precipitate (yield, about 35 per cent.) which was further purified. The dry acid is not very stable but the slightly alkaline solution can be kept for a very long time without appreciable decomposition (Found : Sb, 41.9 ; C, 28.1 ; H, 2.8 ; $C_{14}H_{14}O_8N_2Sb_2$ requires Sb, 41.88 ; C, 28.9 ; H, 2.4 per cent.).

Malonaminodiphenylene-pp-*distibinic acid* (XVIII).—The *sym-pp*-diaminodiphenylmalonamide prepared according to the method of Mistry and Guha (*loc. cit.*), was diazotised and combined with antimony trichloride to a light orange coloured double salt, giving on treatment with alkali a dark-red solution from which acids precipitate the product (yield, about 50 per cent.). The distibinic acid in slightly alkaline solution is quite stable, but in the dry state tends to decompose ; it gives with strong hydrochloric acid a violet colouration which disappears on dilution (Found : Sb, 41.2 ; C, 30.4 : H, 2.2 ; $C_{15}H_{16}O_8N_2Sb_2$ requires Sb, 40.88 ; C, 30.2 ; H, 2.7 per cent.).

Succinaminodiphenylene-pp-*distibinic acid* (XIX).—*sym-pp*-Diaminodiphenylsuccinamide (Mistry and Guha, *loc. cit.*) gave a deep orange antimony double salt which on alkali treatment and subsequent acidification yields (about 50 per cent.) a brown colloidal acid (Found : Sb, 40.1 ; C, 30.9 ; H, 2.9 ; $C_{16}H_{18}O_8N_2Sb_2$ requires Sb, 40.0 ; C, 31.3 ; H, 3.0 per cent.).

sym-*Carbohydrazinodiphenylene*-pp-*distibinic acid* (XX).—*pp'*-Diaminodiphenylcarbohydrazide, prepared from the corresponding dinitro-compound (Mistry and Guha, *loc. cit.*) by reduction with zinc dust and acetic acid, was tetrazotised and combined with antimony chloride. The bright orange double salt on alkali treatment and subsequent acidification gave a dark brown colloidal precipitate (yield, about 30 per cent.) which was further purified. In all its properties it resembled the previously described distibinic acids (XVII-XIX), except that the dry acid decomposed much more rapidly than the other compounds (Found : Sb, 41.6 ; C, 26.4 ; H, 2.8 ; $C_{13}H_{16}O_7N_4Sb_2$ requires Sb, 41.6 ; C, 26.7 ; H, 2.74 per cent.).

sym-pp'-*Diaminodiphenylhydrazodicarbonamide*.—A mixture of hydrazodicarbonamide (1 mol.) prepared according to Thiele (*Annalen*, 1892, **271**, 128) and acetyl-*p*-phenylenediamine (2 mol.) was heated with amyl alcohol under reflux till the evolution of ammonia, vigorous at first, came to an end. The solid was extracted with alcohol, boiled with dilute hydrochloric acid for one hour, and the extract freed from unchanged hydrazodicarbonamide by filtration. The filtrate on evaporation to dryness gave the hydrochloride as violet plates. The free base, liberated by sodium acetate, is greyish-blue, m.p. above 370° ; yield, 40 per cent. (Found : N, 27.92 ; $C_{14}H_{16}O_2N_6$ requires N, 28.0 per cent.).

sym-pp'-*Diacetyldiaminodiphenylazodicarbonamide* was obtained and purified as in the foregoing case by the action of azodicarbonamide with acetyl-*p*-phenylenediamine (m.p. above 370° ; yield, 40 per cent.). The free base was deep blue and did not melt at 350° (Found : N, 27.8 ; $C_{14}H_{14}O_2N_6$ requires N, 28.1 per cent.).

Hydrazodicarbonaminodiphenylene-pp-*distibinic acid* (XXI).—The yellow double salt obtained in the usual way was treated with alkali under ice-cooling, and the brown solution on acidification gave a very poor yield of the brown colloidal distibinic acid (Found : Sb, 39.9 ; $C_{14}H_{16}O_8N_4Sb_2$ requires Sb, 39.8 per cent.).

Hydrazobenzene-pp'-*distibinous oxide* (XXII).—*pp*-Diaminohydrazobenzene was prepared from the azo-compound which in its turn was prepared by the method of Noelting and Binder (*Ber.*, 1887, **20**, 3015). The reduction of the azo-compound was effected by alcoholic ammonium sulphide, and the hydrazo-compound after crystallisation from alcohol melted at 144°. The hydrazo-compound was mixed with antimony trichloride and diazotised, the brownish yellow double compound on alkali treatment giving a dark brown, insoluble product, the glacial acetic acid extract of which gave the distibinous oxide (also in very poor yield) as a brown amorphous powder (Found : Sb, 54.5 ; $C_{12}H_{10}O_2N_2Sb_2$ requires Sb, 53.2 per cent.).

p-*Nitrobenzoyl*-p'-*acetylaminoanilide*, $NO_2.C_6H_4.CO.NH.C_6H_4.NHAc$.—A mixture of *p*-nitrobenzoyl chloride (12 g.) and acetyl-*p*-phenylene diamine (7 g.) was heated in a hard glass tube at 125° for two hours, the product being extracted several times with dilute sodium hydroxide solution until a sample ceased to give a precipitate of nitrobenzoic acid with hydrochloric acid. The greenish yellow residue after being washed with alcohol, in which it was completely insoluble, was crystallised from pyridine, m.p. 293° (decomp.). Hydrolysis and reduction was effected by heating it on the water bath for two hours with stannous chloride and hydrochloric acid. Tin was removed from the filtered solution by hydrogen sulphide and the clear solution after removal of stannous sulphide gave the hydrochloride on evaporation.

Benzanilide-pp'-*distibinous oxide* (XXIII).—The hydrochloride (2 g.) was mixed with antimony trichloride and diazotised, the yellow double salt on alkali treatment giving an insoluble brown product in very poor yield. Extraction with glacial acetic acid left the pure distibinous oxide (Found : Sb, 50.7 : $C_{13}H_9O_3NSb_2$ requires Sb, 51.8 per cent.).

Triphenylphosphine-mmm-*tristibinic acid* (XXIV).—Triphenylphosphine was prepared according to the method of Pfeiffer, Heller and Pitsch (*Ber.*, 1904, **37**, 4621) giving with the following modification a better yield. Addition of the ethereal solution of phosphorus trichloride to phenyl magnesium bromide was made under ice-cooling during four hours. The product, m.p. 78°, was obtained in 95 per cent. yield.

Nitration of triphenylphosphine was effected by the method of Michaelis and Soden (*Annalen*, 1885, **229**, 324). The nitrated product tended to form a sticky mass which, however, on being triturated with an aqueous solution of urea became quite loose and flocculent and after crystallisation from acetic acid melted at 241-242°. Michaelis and Soden regarded it (m.p. 242°) as a *para*-substitution product, but Challenger and Wilkinson showed it to be the *meta*-derivative (*J. C. S.*, 1924, **125**. 2675).

Reduction of the trinitro-compound was conducted by heating it on the water bath with zinc dust and acetic acid. On dilution with water and addition of alkali the precipitate of triamine was practically pure and was crystallised from alcohol, m.p. 255°. A hydrochloric acid solution of *mmm*-triaminotriphenylphosphine (5 g.) and antimony trioxide (7 g.) was diazotised

with sodium nitrite (3 g.) and the yellow double salt thus obtained treated with 5*N* alkali under ice-cooling. The brown solution on acidification yielded the colloidal tristibinic acid which required nearly two days to settle, but addition of common salt hastened the process of coagulation considerably; it was further purified in the usual manner.

Estimation of antimony was effected by mixing the substance (about 0.2 g.) with concentrated sulphuric acid (10 c.c.) and anhydrous potassium sulphate (3 g.), then heating the mixture very gently and cautiously till the solution became colourless. On dilution with water, 15 c.c. of hydrochloric acid was added and the antimony sulphide precipitated with hydrogen sulphide was dissolved in very dilute sulphuric acid and oxidised with potassium permanganate, excess of which was removed by boiling with hydrochloric acid; the colourless solution was cooled, mixed with potassium iodide (2 g.) and titrated against standard thiosulphate using starch as an indicator (Found: Sb, 46.8: $C_{18}H_{18}O_9PSb_3$ requires Sb, 47.2 per cent.).

Triphenylarsine-mmm-*tristibinic acid* (XXV).—Triphenylarsine was prepared in the same manner as the phospline, nitration and reduction being carried out by the method of Michaelis (*Annalen*, 1902, **321**, 180). A mixture of the hydrochloric acid solution of the triamine and the required quantity of antimony trichloride on diazotisation gave a yellow double compound which on treatment with 5*N* alkali under efficient ice-cooling gave a brown solution from which the colloidal acid was liberated and purified in the usual manner. Estimation of arsenic and antimony was conducted according to the modified method of Fargher (*J. C. S.*, 1919, **115**, 992. Found: Sb+As, 54.28; $C_{18}H_{18}O_9AsSb_3$ requires Sb+As, 53.8 per cent.).

Triphenylstibine-mmm-*tristibinic acid* (XXVI).—Triphenylstibine was prepared by the method described in Organic Synthesis, Vol. VII, 80, while the nitration and reduction were effected by the method of Morgan and Micklethwait (*J. C. S.*, 1911, **99**, 2299). The yellow double salt on alkali treatment gave a brown solution which on acidification gave the tristibinic acid which did not show the colour reaction of the distibinic acids (Found: Sb, 55.9; $C_{18}H_{18}O_9Sb_4$ requires Sb, 56.3 per cent.). The tristibinic acids here described are all very unstable and in the dry state decompose very easily.

Summary.

With a view to throwing some further light on the chemotherapy of organic antimonials a large number of aromatic di- and polyamines having the amino-groups attached to the same or different phenyl radicals have been stibinated according to the well-known method of Bart and Schmidt. Contrary to the general rule that aromatic amines on stibination yield only the corresponding stibinic acids, quite a large number of di- and polyamines have now been found to yield di- and poly-stibinous oxides (IV-VII, X-XII, XIV-XVI, XXII, XXIII). The distibinous oxides are not affected by mild oxidising agents such as hydrogen peroxide, and are decomposed when subjected to more drastic processes of oxidation. On reduction, however, they give rise to highly coloured products which could not be sufficiently purified owing to their unstable nature, but are probably distibino-compounds.

In one case, namely, *pp*-diaminodiphenylurea, a compound has been obtained which in all probability is a secondary monostibinic acid (XIII).

The work is being continued, and although it is not possible at this stage to formulate any definite rule underlying the formation of stibinous oxides and stibinic acids, it can, however, be said that—

(1) *pp*-Amino-groups in diphenyl give stibinous oxides.

(2) The groups CO and C(OH) connecting two or more phenyl radicals aid in converting *p*-amino-compounds into stibinic acids, whereas the CH_2 group favours the formation of stibinous oxides.

(3) Connecting links involving nitrogen besides carbon, when oxygenated, also yield stibinic acids, whereas in absence of oxygen the stibinous oxides are produced. Only one exception to this rule, namely, diaminobenzanilide, which yields the distibinous oxide, has yet been observed.

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