2. *The Configuration of Heterocyclic Compounds. Part XI. Preparation of Phenoxstibines and Resolution of* 10-p-*Carboxyphenyl*-2-*methylphenoxstibine.*

By (Miss) I. G. M. Campbell.

The preparation of several phenoxstibines by the reaction of phenylstibinous halides on the "double" Grignard reagent from 2 : 2′-dibromo-4-methyldiphenyl ether is described. The resolution of 10-*p*-carboxyphenyl-2-methylphenoxstibine has been accomplished by means of the strychnine salts, and the *d*- and the *l*-acid, $[\alpha]_D \pm 77°$ in chloroform, are stable in chloroform and benzene at the boiling point but racemise slowly in boiling alcohol. These results indicate that the molecule is folded about the O–Sb axis in order to accommodate the intervalency angle of antimony, and that the folding is sufficiently rigid to produce optical isomers of considerable stability. The *dl*-acid was tested for trypanocidal properties and was shown to possess little activity compared with "stibophen."

Parts I—X of this series (Turner, Lesslie *et al.*, *J.*, 1934, 1170; 1935, 1051, 1268; 1936, 730; 1937, 444; 1938, 29, 37, 404, 1001; 1939, 1050) describe the resolution of phenoxarsines and the unsuccessful attempts to resolve phenox-thionine-, -selenine-, -tellurine-, and -thianthren-carboxylic acids. To explain these results it was suggested that the phenoxarsine molecule was rigidly folded about the O–As axis, whereas the other molecules, though folded, were flexible. The stability of the optically active phenoxarsines was ascribed to the mutual effect of the folded ring system and the third group attached to the tervalent arsenic atom. It was considered probable that phenoxstibines would exhibit similar stability and that it would be of interest to compare the two types of compound, especially as the stereochemistry of antimony compounds has been little studied.

Although much information has been obtained on the stereochemistry of 3-covalent nitrogen, phosphorus, and arsenic by both physical and organic methods, evidence for the configuration of 3-covalent antimony compounds is relatively meagre. *X*-Ray methods have been used to elucidate the structure of metallic antimony and some of its inorganic compounds, and the trihalides have been studied in the vapour state by electron diffraction, but little information on tervalent organic antimony compounds is available. No attempted resolution of antimony compounds has been reported.

Physical measurements show that the molecules of antimony trihalides are pyramidal with

interbond angles of about 100°, and that in quinquevalent compounds such as the trimethylstibine dihalides the molecule has the form of a trigonal bipyramid with the antimony atom and the three methyl groups in the central plane and the halogens at the two remaining apices (Wells, *Z. Krist.*, 1938, **99**, 367). The dipole moment of triphenylstibine dichloride is zero (*Z. anorg. Chem.*, 1943, **250**, 257; cf. *J. Amer. Chem. Soc.*, 1942, **64**, 173), which confirms the bipyramidal structure for compounds of this type. The dipole moments of triphenyl-phosphine, -arsine, and -stibine are 1·45, 1·07, and 0·57 × 10^{-18} e.s.u. respectively, suggesting a progressive reduction in the height of the pyramidal molecule (*Z. physikal. Chem.*, 1932, *B*, **19**, 401). As it seemed unlikely that resolution of a simple stibine containing three different groups would be successful unless the inversion of this pyramidal configuration was greatly inhibited, it was decided to attempt the resolution of a phenoxstibine (I) where the antimony atom was a member of a heterocyclic ring.

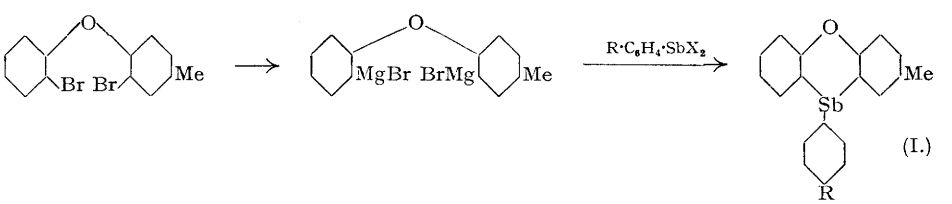
The resolution of several phenoxarsinecarboxylic acids into optically stable enantiomers (Lesslie and Turner, *loc. cit.*) and the isolation of two geometrical isomers of 5 : 10-di-*p*-tolyl-5 : 10-dihydroarsanthren (Chatt and Mann, *J.*, 1940, 1184) leave little doubt that this type of molecule is folded about the central axis. One can suggest an approximate configuration for the molecule by calculation from the geometry of the figure. The radii of aromatic carbon, oxygen, and antimony being taken as 0·70, 0·74, and 1·41 A., respectively, and the oxygen angle (θ) as 120°, 130°, or 140°, the values calculated for the antimony angle (ϕ) and the angle of fold (ψ) are as follows :

θ	120°	130°	140°
ϕ	88·7	94·2	98·7
ψ	133·0	147·4	168·7

From these figures it appears possible that the angle of fold is in the region of 147°, for an oxygen angle of 130° is probable and the value of 94° for the interbond angle of antimony is not far removed from that found in crystalline antimony and its trihalides. Evidence that the molecule of 10-*p*-carboxyphenyl-2-methylphenoxstibine is, in fact, folded is given in the following description of its resolution into optical enantiomers, though the racemisation of the active acid in boiling alcohol suggests that the folding is considerably less rigid than in the case of the phenoxarsines.

The preparation of phenoxstibines presented some difficulty. At first the synthesis was attempted by the method used by Lesslie and Turner (*J.*, 1934, 1170) for the preparation of phenoxarsines, but the introduction of antimony into 2-amino-4′-methyldiphenyl ether by the Bart–Schmidt process gave yields of only 5—7% of the stibonic acid. The modifications suggested by Morgan (*Proc. Roy. Soc.*, 1930, *A*, **127**, 1; 1933, *A*, **143**, 38) did not improve the yield. Equally low yields of 2-*p*-tolyloxyphenylstibinous chloride were obtained when the diazonium antimony chloride double salt was treated, in dry acetone, with copper powder at — 60° by Nesmejanow's method (*Ber.*, 1929, **62**, 1010) for the introduction of mercury. Cyclisation of the stibonic acid could not be effected by any of the usual reagents and the stibinous chloride was not cyclised by vacuum distillation. Attempts to introduce antimony by modification of the method used successfully for the introduction of tellurium, *i.e.*, the reaction of antimony trichloride on 2-*p*-tolyloxyphenyl mercurichloride, failed.

A synthesis for phenoxstibines was finally achieved by the simultaneous introduction of antimony and ring closure. 2 : 2′-*Dibromo*-4-*methyldiphenyl ether*, in concentrated ethereal



(I.)

solution, reacted slowly with magnesium turnings, activated by a few drops of methyl iodide, to form a " double " Grignard reagent in about 80% yield. 10-*Phenyl*-2-*methylphenoxstibine* (I, R = H) was obtained in 35% yield by the reaction of phenylstibinous iodide with this reagent. Unfortunately, oxidation of the methyl group to the carboxyl group wanted for resolution experiments proved impracticable. 10-p-*Cyanophenyl*-2-*methylphenoxstibine* (I, R = CN) was prepared in a similar way, but the cyanide group could not be hydrolysed to carboxyl without affecting the antimony ring system. 10-p-*Bromophenyl*-2-*methylphenox-*

stibine (I, R = Br), also obtained in 30—35% yield, could not be induced to form a Grignard reagent. Finally, the reaction of p-*carbethoxyphenylstibinous chloride* with the double Grignard reagent produced the *carbethoxyphenylphenoxstibine* (I, R = CO_2Et), but the yields never exceeded 15%. Hydrolysis of the ester with alcoholic sodium hydroxide gave the acid.

All these phenoxstibines are well-crystallised, stable compounds. The ring system is sensitive to acids, especially when the antimony atom is quinquevalent. For instance, reduction of the stibine dichlorides in acid suspension with sulphur dioxide can result in ring fission or complete elimination of the antimony with the production of phenyl tolyl ether if temperature and sulphur dioxide concentration are not carefully controlled. Alkali, on the other hand, appears to have no effect. The cyanostibine was regained unchanged from fused potassium hydroxide and also after boiling with 30% aqueous or alcoholic sodium hydroxide.

10-p-*Carboxyphenyl*-2-*methylphenoxstibine* forms salts with all the common alkaloids and with α-phenylethylamine. Strychnine was chosen as the resolving agent because preliminary experiments indicated that the diastereoisomeric salts differed widely in solubility, and the resolution proved comparatively easy when the conditions of preparation and of recrystallisation of the salts were carefully regulated. Prolonged boiling of suspensions of the less soluble diastereoisomeric salt in alcohol resulted in separation of free acid as well as salt, shown by anomalous rotations and the lowering of carbon content on analysis. The difficulty was overcome by dissolving the salt in the minimum volume of boiling chloroform and adding alcohol at 60°. The optically pure *d*-acid strychnine *salt*, $[\alpha]_D$ + 34·5° in chloroform, was very sparingly soluble in alcohol. Purification of the more soluble salt by recrystallisation from boiling alcohol led to second-order asymmetric transformation; in one instance a fraction of salt with $[\alpha]_D$ — 18° was boiled with ethyl alcohol for 30 minutes and an almost equal weight of salt with $[\alpha]_D$ + 17° was regained. In fact unless the fractions of impure *l*-acid strychnine *salt* separating from the original preparation had a specific rotation of — 50° or more, the optically pure material was not obtained. Recrystallisation of fractions of salt with $[\alpha]_D$ — 50° from methyl alcohol raised the rotation to $[\alpha]_D$ — 60·7°. The *acids* regained from the two diastereoisomeric salts had $[\alpha]_D$ + 77·5° and — 77·2° and were stable in chloroform, benzene, and alcohol at room temperature and in the first two solvents at their boiling point, but racemised slowly in boiling alcohol, the specific rotation falling from + 87·64° to + 34·40° after 13 hours' boiling. Solutions of the active acids in 0·1N-sodium hydroxide, -ammonium hydroxide, and -potassium hydrogen carbonate were very faintly opalescent so reliable polarimetric readings could not be taken, but acid regained from the sodium hydroxide solution after one hour's boiling had $[\alpha]_D$ + 55·30°, and that regained from ammonium salt solution which had been kept at room temperature for 14 days had $[\alpha]_D$ + 12·51°.

The comparative ease of racemisation is surprising in view of the pronounced optical stability of the phenoxarsines, although no direct comparison can be made as the phenoxstibine under discussion is not the antimony analogue of any of the known optically active phenoxarsines. Two factors may contribute to the ease of racemisation in this case; first, the larger diameter of the antimony atom may result in an angle of fold closer to 180° and, secondly, the heavy polar *p*-carboxyphenyl group in the 10-position may encourage inversion of the pyramidal configuration of the antimony atom.

Dr. J. Ungar, of the Department of Experimental Medicine, Glaxo Laboratories, Greenford, very kindly undertook to test the *dl*-acid for trypanocidal activity. The compound was tested in aqueous solution (pH 7·8—8·0) by the method described by Goodwin (*J. Pharmacol.*, 1944, **81**, 224). Mice of standard weight (20 g.) were infected with a standard dose of *Trypanosoma equiperdum* and injected intravenously with 0·5 ml. of solutions of *dl*-acid containing 1·0, 0·5, 0·1, or 0·05 mg. of antimony. The peripheral blood of each infected mouse was examined for the presence of trypanosomes at intervals of 24 hours. The results showed that *p*-carboxyphenyl-2-methylphenoxstibine had low toxicity but very little trypanocidal activity compared with "stibophen."

Experimental.

Carbon and hydrogen analyses are by Drs. Weiler and Strauss, Oxford. M. p.'s are uncorrected. Rotations were observed in A.R. chloroform at room temperature in 2-dm. tubes, unless otherwise stated.

2-Bromo-2'-nitro-4-methyldiphenyl Ether.—Half-molar quantities of 3-bromo-*p*-cresol (Zincke and Wiederhold, *Annalen*, 1902, **320**, 203) and *o*-chloronitrobenzene were condensed under the conditions recommended by Henley (*J.*, 1930, 1222). The *ether*, recrystallised from alcohol, separated in thin, hexagonal plates, m. p. 71° (70—75% yield) (Found: Br, 26·0. $C_{13}H_{10}O_3NBr$ requires Br, 25·9%).

2-Bromo-2'-amino-4-methyldiphenyl Ether.—The *amine* (70 g.) was obtained by reduction of the nitro-ether (100 g.) with an equal weight of iron filings and acidified water at 100°. It was extracted

from the iron with boiling alcohol and distilled after removal of the solvent, forming a thick colourless oil, b. p. 180—182°/3 mm., which crystallised, m. p. 45—47° (Found : Br, 28·6. $C_{13}H_{12}ONBr$ requires Br, 28·75%).

2′-Bromo-2-nitro-4-methyldiphenyl Ether.—Chloro-*m*-nitrotoluene was condensed with *o*-bromophenol by Henley's method. Half-molar quantities produced 102 g. of *ether* after recrystallisation from alcohol, from which it separated as pale yellow, rectangular plates, m. p. 70° (Found : Br, 26·2%).

2′-Bromo-2-amino-4-methyldiphenyl Ether.—Reduction of the nitro-ether (100 g.) with an equal weight of iron gave 80 g. of the *amine* (Found : Br, 28·9. $C_{13}H_{12}ONBr$ requires Br, 28·8%), b. p. 188—192°/4 mm., which did not crystallise. Its hydrochloride had m. p. 186—187°.

2 : 2′-Dibromo-4-methyldiphenyl Ether.—The amino-group in each of the foregoing two bases was replaced by bromine by the Sandmeyer, Gattermann, and perbromide procedures. There was no significant difference in the yields from the two, and the perbromide method gave the highest yields when the following conditions were used. The base (55·6 g., 0·2 mol.) was dissolved in 50 c.c. of concentrated hydrochloric acid and 100 c.c. of water, and diazotised with sodium nitrite (14 g.). To the filtered diazonium salt solution, 48 g. (0·3 mol.) of bromine in 140 g. of hydrobomic acid (48%) were added slowly with vigorous stirring. The precipitated perbromide was filtered off, washed well with ice-cold water, and dropped, in small portions, into hot glacial acetic acid. When decomposition was complete the reaction mixture was poured into 2 l. of water, extracted with chloroform, and the extract washed with water and 2N-sodium hydroxide. After removal of the chloroform the residue was distilled at 1 mm. pressure, b. p. 160—200°. Redistillation with a fractionating column gave the *ether* as the main fraction, an almost colourless oil, b. p. 168—171°/0·5 mm. (37·6 g., 55%) (Found : Br, 46·5, 46·8. $C_{13}H_{10}OBr_2$ requires Br, 46·7%).

Preparation of the Grignard Reagent.—Freshly distilled 2 : 2′-dibromo-4-methyldiphenyl ether (17·1 g., 0·05 mol.) was warmed to 30—35° and added slowly to 5·0 g. (0·105 mol.) of magnesium turnings covered with 100 c.c. of dry ether and activated with 3 or 4 drops of methyl iodide. During this addition the flask was kept sufficiently warm to reflux the ether. No obvious reaction occurred until the addition was almost complete. A second portion of 17·1 g. of dibromo-ether in 60 c.c. of ether was added slowly, and the reaction become more vigorous. The whole addition required about 2 hours, and complete solution of the magnesium considerably longer. Reaction was allowed to proceed overnight, the flask being kept warm. The mixture was then cooled to room temperature and filtered from a small quantity of unchanged magnesium into a three-necked flask. The yield of the " double Grignard " reagent was about 80% as shown by decomposition of one batch with dilute acid, pure phenyl *p*-tolyl ether being obtained in 80% yield. The formation of this Grignard reagent presented no difficulty provided the 2 : 2′-dibromo-4-methyldiphenyl ether was freshly distilled, but if it had been kept for 24 hours it reacted very slowly or not at all.

10-Phenyl-2-methylphenoxstibine.—Phenylstibinous iodide (45 g., 0·1 mol.), prepared by Schmidt's method (*Annalen*, 1920, **421**, 218), was dissolved in 400 c.c. of benzene and added slowly to the Grignard reagent from 34·2 g. (0·1 mol.) of dibromo-ether in the 3-necked flask, cooled in a freezing mixture and stirred with a stream of nitrogen. The addition was stopped when the yellow colour of the iodide was no longer discharged, *i.e.*, when 38—40 g. had been added. Most of the ether was removed by distillation, and the residual benzene solution was cooled and treated with ice and dilute hydrochloric acid. The benzene layer was washed with 2N-hydrochloric acid and water. The latter produced a small quantity of finely divided solid which tended to give an emulsion. Distillation of the residue after removal of the benzene gave as the main fraction 32 g. of pale yellow, viscous oil, b. p. 200—210°/0·5 mm. This consisted of the phenoxstibine and polymeric material. As no crystallisation could be induced, the compound was chlorinated in ice-cold carbon tetrachloride (80 c.c.), and the dichloride separated as colourless prisms; recrystallisation from carbon tetrachloride gave 20 g. of *10-phenyl-2-methylphenoxstibine dichloride*, m. p. 112° (decomp.). Recrystallisation from toluene produced long, flat plates, m. p. 104—105°, and from petroleum (b. p. 100—120°) small prisms, m. p. 140—142°. The last is the only solvent from which the compound separates free from solvent of crystallisation (Found : Sb, 26·7; Cl, 15·75. $C_{19}H_{15}OCl_2Sb$ requires Sb, 26·9; Cl, 15·7%).

The dichloride (6 g.) was dissolved in 150 c.c. of absolute alcohol, and ammonia (*d* 0·88) added dropwise until a precipitate of the oxide began to appear. The reaction mixture was heated to b. p., and hydrogen sulphide was passed in until the solution became yellow. On standing in ice, the colour vanished and feathery needles separated. These were recrystallised from light petroleum (b. p. 40—60°) and had m. p. 62—63°, 4 g. The yield of *stibine*, based on the phenylstibinous iodide used, was 30—35% (Found : C, 59·7; H, 4·1. $C_{19}H_{15}OSb$ requires C, 59·9; H, 4·0).

Attempted oxidation of the 2-methyl group to a carboxyl group failed with alkaline or neutral permanganate, dearylation occurring (cf. Schmidt, *Annalen*, 1922, **429**, 141). Acid oxidising agents such as chromic acid in glacial acetic acid resulted in fission of the heterocyclic ring system.

p-Cyanophenylstibinous Chloride and Iodide.—*p*-Aminobenzonitrile was made by reduction of *p*-nitrobenzonitrile with stannous chloride in hydrochloric acid, and the introduction of antimony was effected by Gibson and Kingan's method (B.P. 569,037, 10.6.40). The base (24 g., 0·2 mol.) in 50 c.c. of concentrated hydrochloric acid and 100 c.c. of water was diazotised with 14 g. of sodium nitrite. The filtered solution was added to 30 g. of antimony trioxide in 150 c.c. of concentrated hydrochloric acid at — 5°, and the precipitated double salt filtered off and washed with ice cold alcohol. It was suspended in a mixture of 250 c.c. of 95% alcohol and 50 c.c. of absolute alcohol which had been saturated with hydrogen chloride. Copper bronze (0·5 g.) was added, and the mixture stirred mechanically. Evolution of nitrogen started immediately at 0° but did not become vigorous until the heat of the reaction had raised the temperature to 30°. Decomposition of the double salt was complete within an hour, and on pouring the resultant solution into water the stibonic acid was precipitated in a condition sufficiently pure for the preparation of the stibinous chloride without purification through the ammonium chloride double salt. Reduction was carried out at — 5° in hydrochloric acid with stannous chloride. Since complete drying of the stibonic acid reduced its solubility in hydrochloric acid, and heating,

necessary to obtain solution of the dried acid, resulted in slight decomposition, the reduction was carried out with the freshly precipitated moist acid. Stannous chloride (80 g.) was added in small quantities during ½ hour to a solution of 80 g. of the moist acid in 160 c.c. of hydrochloric acid (*d* 1·126). The stibinous chloride began to separate before the addition of stannous chloride was completed. The reaction mixture was kept in ice for a further 2 hours before filtration. The *chloride* was dried on tile and recrystallised immediately from carbon tetrachloride, from which it separated as colourless needles, m. p. 74—75° (Found: Sb, 41·0. $C_7H_4NCl_2Sb$ requires Sb, 41·2%).

To obtain the *iodide*, the moist acid was dissolved in twice the volume of hydrochloric acid used in the last experiment and reduced in the same way. The stibinous chloride remained in solution, and saturated potassium iodide solution was added till no further precipitation occurred. The bright yellow iodide was filtered off, dried on tile, and immediately recrystallised from carbon tetrachloride; m. p. 98·5—99°, yield 40—50% (Found: Sb, 25·55. $C_7H_4NI_2Sb$ requires Sb, 25·5%).

10-p-*Cyanophenyl*-2-*methylphenoxstibine*.—The preparation of this compound was carried out in the same way as that of the 10-phenyl derivative, 0·05-molar quantities being used. Distillation gave a main fraction of pale yellow, viscous oil (16·9 g.), b. p. 200—240°/0·5 mm. No crystallisation occurred in the original experiment. Chlorination of the oil in carbon tetrachloride at 0° gave the dichloride, m. p. 180—181°, from which the stibine was obtained by hydrogen sulphide reduction in alcoholic ammonia solution. In subsequent preparations the distillate was seeded with the pure stibine which induced partial crystallisation. The crystals were separated from sticky polymeric material with alcohol–light petroleum (b. p. 40—60°) (4 : 1), and when recrystallised from petroleum separated in rosettes of needles, m. p. 82° (7·1 g., 34%) (Found: C, 59·6; H, 3·6; Sb, 30·05. $C_{20}H_{14}ONSb$ requires C, 59·15; H, 3·5; Sb, 30·0%).

Hydrolysis of the *cyanide* was impracticable. Acid hydrolysis eliminated antimony and phenyl *p*-tolyl ether was isolated, and from alkaline hydrolysis the unchanged cyanide was regained. The compound is exceptionally stable to alkali; 1 g. was held for 15 minutes in 5 g. of molten potassium hydroxide and was regained unchanged.

10-p-*Bromophenyl*-2-*methylphenoxstibine*.—*p*-Bromoaniline was converted into *p*-bromophenylstibinous iodide by the method described for the *p*-cyano-compound and obtained in 35—40% yield, m. p. 122—123° (cf. Blicke and Oakdale, *J. Amer. Chem. Soc.*, 1933, **55**, 1198). The cyclic stibine was prepared by the method described above, using 0·05-molar quantities. Distillation of the reaction product gave a very viscous, pale yellow oil, b. p. 220—260°/0·3 mm. (18·4 g.). Chlorination of this in ice-cold carbon tetrachloride solution produced 13·7 g. of dichloride, m. p. 202°, from which the stibine was obtained by reduction with hydrogen sulphide in alcoholic ammonia solution. The pure stibine was used to seed the distillate from further preparations and partial crystallisation occurred. The crystals were separated from by-products with alcohol–light petroleum (b. p. 60—80°) (4 : 1) and recrystallised from alcohol. The *stibine* is sparingly soluble in alcohol and separates from it in rosettes of colourless needles, m. p. 116° (yield 30—35%) (Found: C, 49·7; H, 3·1; Sb, 26·4. $C_{19}H_{14}OBrSb$ requires C, 49·6; H, 3·1; Sb, 26·5%). An ethereal solution of the bromostibine was added to magnesium turnings activated by iodine or by methyl iodide, but no formation of a Grignard reagent could be induced.

p-*Carbethoxyphenylstibinous Chloride*.—When ethyl *p*-aminobenzoate was converted into the corresponding stibonic acid by the usual Bart–Schmidt reaction, the ester group was partially hydrolysed (cf. Clark, *J.*, 1932, 1826). The carboxyl group was re-esterified by suspending the acid (10 g.) in absolute alcohol (50 c.c.), passing in hydrogen chloride till solution was complete, and then boiling the solution under reflux for an hour. *p*-Carbethoxyphenylstibonic acid was precipitated on pouring the alcoholic solution into water. When antimony was introduced by Gibson and Kingan's method (*loc. cit.*) no hydrolysis of the ester group occurred and a yield of 50—55% of the stibonic acid was obtained after purification through the ammonium chloride double salt.

Reduction.—When the stibonic acid (40 g., moist) was dissolved in hydrochloric acid (60 c.c., *d* 1·126), the tetrachloride separated as a viscous oily layer and satisfactory reduction could only be obtained if the reaction mixture, kept below 0°, was shaken vigorously after each addition of stannous chloride, 40 g. in all being required. The *dichloride* was filtered off after standing for 2 hours at 0°, dried on tile, and recrystallised from carbon tetrachloride, in which it is rather insoluble, or from ethylene dichloride. It separated from the latter in flat elongated plates, m. p. 127°, and was highly sternutatory (Found: Sb, 35·5. $C_9H_9O_2Cl_2Sb$ requires Sb, 35·7%).

Preparation of the stibinous iodide by the method used previously was impracticable because of the very low solubility of the stibinous chloride in hydrochloric acid. Attempts to prepare the iodide by solution of the pure chloride in dry acetone and addition of the calculated quantity of sodium iodide in the same solvent, followed by removal of the precipitated sodium chloride and evaporation of the solvent under reduced pressure, afforded an *iodide* which was very insoluble in organic solvents, except alcohol and ethyl acetate from which it did not crystallise. Small quantities obtained in crystalline form melted indefinitely and showed a deficit of antimony (Found: Sb, 22·4, 22·3. $C_9H_9O_2I_2Sb$ requires Sb, 23·2%). The stibinous chloride was therefore used in the reaction with the Grignard reagent. It has distinct disadvantages because of rather low solubility and because completion of the reaction could not be seen, as in previous experiments, by discharge of the yellow colour of the iodide.

10-p-*Carbethoxyphenyl*-2-*methylphenoxstibine*.—The Grignard reagent prepared from 17·1 g. (0·05 mol.) of dibromo-ether was filtered into a three-necked flask, diluted with ether to 250 c.c., cooled in a freezing mixture, and stirred with a stream of nitrogen while a solution of *p*-carbethoxyphenylstibinous chloride (14 g., 0·04 mol.) in 250 c.c. of dioxan was added during 15—20 minutes. A thick, cream-coloured mass was precipitated. The mixture was allowed to reach room temperature and boiled under reflux for 1 hour, during which the precipitate became much more crystalline; it was then cooled in a freezing mixture and treated with ice and dilute hydrochloric acid. The addition of acid produced an orange-red colour which was partly removed on washing the ethereal layer with water to remove dioxan. Emulsions were frequent at this stage owing to separation of small quantities of water and ether-

insoluble material. The reddish-brown glass obtained after the removal of ether could not be distilled without decomposition at 0·25 mm. pressure, but the stibine was obtained from it by repeated extraction with light petroleum (b. p. 40—60°). A simpler method of isolation was to distil off ether until about 40—50 c.c. remained, and allow the stibine to crystallise from this. The *stibine*, recrystallised from alcohol, separated in flat needles, m. p. 136—137° (2·0 g., 15%) (Found: C, 58·2; H, 4·3; Sb, 26·8. $C_{22}H_{19}O_3Sb$ requires C, 58·3; H, 4·2; Sb, 26·9%).

10-p-*Carboxyphenyl*-2-*methylphenoxstibine*.—The ester (5 g.) was dissolved in 100 c.c. of 5% alcoholic potassium hydroxide and boiled under reflux for ½ hour. The solution was poured into 500 c.c. of water and acidified with dilute hydrochloric acid. The precipitated *acid* was filtered off, dried, and recrystallised from alcohol, separating in rosettes of small needles (4·1 g.), m. p. 201° (Found: C, 56·5; H, 3·6; Sb, 28·8. $C_{20}H_{15}O_3Sb$ requires C, 56·5; H, 3·6; Sb, 28·65%).

Resolution with Strychnine.—Several experiments on the resolution of the *dl*-acid with strychnine were carried out, including one method of partial precipitation. All of these permitted the isolation of pure *d*-acid strychnine salt but most failed to produce the *l*-acid salt in a state of optical purity. Unfortunately, neither the cinchonine nor the cinchonidine salt possessed the reverse solubility relationship, so it was impossible to complete the resolution by their use, and brucine proved of no value as a resolving agent because the salts always separated initially as an oil. Quinine gave an apparently incomplete resolution, the significance of which remains doubtful and which will be further investigated. Finally, a complete resolution was obtained with strychnine as follows.

The *dl*-acid (5·25 g.) and strychnine (4·13 g.) were dissolved respectively in 300 c.c. of warm alcohol and 50 c.c. of chloroform, and the solutions mixed. The first fraction, F1 (5·0 g.), had $[\alpha]_D$ + 17·0° (*c*, 0·501). On removal of the chloroform under vacuum below 25°, F2 (2·3 g.) separated, $[\alpha]_D$ − 59·11° (*c*, 0·515). F3 (1·4 g.,), $[\alpha]_D$ − 41·10° (*c*, 0·510), separated when the mother-liquor was concentrated to 150 c.c. by distillation at 12 mm., and further concentration to 50 c.c. gave, on standing, F4 (0·6 g.), $[\alpha]_D$ − 19·96° (*c*, 0·501). F4 is apparently the *dl*-acid strychnine salt, as a solution of equivalent quantities of the acid and strychnine in chloroform had $[\alpha]_D$ − 19·97° (*c*, 0·545). Three recrystallisations of F1 from alcohol–chloroform gave 2·3 g. of *d*-acid strychnine *salt*, $[\alpha]_D$ + 34·4° (*c*, 0·510), as very small needles, m. p. 218° (Found; C, 64·0; H, 5·0. $C_{41}H_{37}O_5N_2Sb$ requires C, 64·9; H, 4·9%).

F2 after two recrystallisations from methyl alcohol had $[\alpha]_D$ − 60·73° (*c*, 0·510), 1·6 g., which separated as long thin needles, m. p. 100° (decomp.) (Found: C, 63·0; H, 5·0. $C_{41}H_{37}O_5N_2Sb,H_2O$ requires C, 63·3; H, 5·05%). All these salts were optically stable in chloroform solution at room temperature. Prolonged boiling of solutions of the *l*-acid strychnine *salt* in ethyl alcohol during recrystallisation had to be avoided because the resulting salt became less lævorotatory. To obtain evidence of this second-order asymmetric transformation, 0·6 g. of salt with $[\alpha]_D$ − 18·0° was boiled with 20 c.c. of absolute alcohol for 30 minutes, the salt insoluble in this volume was filtered off, and the filtrate allowed to crystallise. The undissolved salt (0·1 g.) had $[\alpha]_D$ + 18·5°, and the salt separating from the filtrate (0·45 g.) had $[\alpha]_D$ + 17·0°. Optically pure *l*-acid strychnine salt was never obtained unless the fraction separating in the original preparation of the salt had approximately $[\alpha]_D$ − 50°, and purification had to be done by quick recrystallisation from the minimum volume of methyl alcohol.

d-10-p-*Carboxyphenyl*-2-*methylphenoxstibine*.—The *d*-acid was obtained by extraction of a chloroform solution of its strychnine salt with 0·5N-hydrochloric acid and removal of the chloroform under reduced pressure. It had $[\alpha]_D$ + 77·50° in chloroform (*c*, 0·555), $[\alpha]_D$ + 89·6° in benzene (*c*, 0·513), and $[\alpha]_D$ + 87·64° in absolute alcohol (*c*, 0·291). No change in rotation occurred when a solution of the active acid in chloroform was kept for 14 days at room temperature, or at 45° for 4 hours, or boiled under reflux for 2 hours. A solution of the acid in benzene was boiled for 1 hour and no change was noticeable. In alcohol, on the other hand, the rotation of the acid decreased on boiling the solution and the following results were obtained (initial rotation, $[\alpha]_D$ + 87·64°):

Time of boiling (hrs.)	1	2	3	5	8	13
$[\alpha]_D$	+77·30°	+68·73°	+61·73°	+53·26°	+46·40°	+34·35°

Change in concentration of the solution occurs by evaporation, so the racemisation does not appear to obey the unimolecular law. Acid recovered from such racemisation experiments was chemically pure (Found: C, 56·3, H, 3·7%). Recrystallisation of the active acid from methyl alcohol was possible without much racemisation; the first fraction to separate had $[\alpha]_D$ + 77·3° but the second had $[\alpha]_D$ + 64·4°. The optically pure *acid* melts at 192° (bath preheated to 180°) (Found: C, 56·65; H, 3·7. $C_{20}H_{15}O_3Sb$ requires C, 56·5, H, 3·6%).

l-10-p-*Carboxyphenyl*-2-*methylphenoxstibine*.—The l-*isomer* was obtained from the more soluble strychnine salt in a similar manner and had $[\alpha]_D$ − 77·2° (*c*, 0·518; chloroform) and − 89·9° (*c*, 0·250; benzene), m. p. 192° (preheated bath) (Found: C, 56·7; H, 3·7%).

Both active acids on solution in dilute alkali (0·05N-NaOH, 0·1N-NH_4OH, and 0·1N-$KHCO_3$) gave solutions which were faintly opalescent. It was impossible to obtain reliable polarimetric readings, but the specific rotations of these solutions appeared to be slightly greater than that of the pure acid in chloroform; *e.g.*, $[\alpha]_D$ + 77·9° in 0·05N-NaOH. This solution was boiled for an hour and the acid regained from it had $[\alpha]_D$ + 55·9°. The ammonium salt was kept at room temperature for 14 days and the acid regenerated from it had $[\alpha]_D$ + 12·5°.

Racemisation apparently occurs on heating in the absence of solvents because the m. p.'s of the active acids ranged from 194° to 198° when observed in a bath heated slowly from room temperature. In a bath pre-heated to 180°, they melted sharply at 192°. The following m. p.'s were obtained with mixtures of the *d*- and the *dl*-acid. The mixtures (inserted at 180°), with the exception of the 50 : 50 mixture, melted over a range of 2—3° and the m. p. given is that of complete fusion.

d-Acid, %	100	90·0	83·3	75·0	66·6	50·0
M. p.	192°	187°	191°	194°	196·5°	201°

The author thanks the Chemical Society and Imperial Chemical Industries Ltd. for grants which defrayed the costs of chemicals and microanalyses respectively. For the tests on trypanocidal activity the author is greatly indebted to Dr. Ungar, of the Department of Experimental Medicine, Glaxo Laboratories, Greenford, Middlesex.

UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, April 15th,* 1946.]