253. *The Configuration of Heterocyclic Compounds. Part I. The Optical Resolution of* 10-*Methylphenoxarsine*-2-*carboxylic Acid.*

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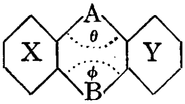
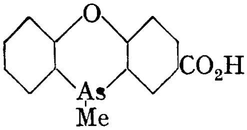
Although the planar configuration of benzene, naphthalene, and anthracene is now established, little is known of the configuration of heterocyclic systems, in which at least two new factors are necessarily introduced, *viz.*, the atomic diameter and the valency angle of the element or elements other than carbon. From the point of view of their application to stereochemical problems, measurements of atomic diameter are, on the whole, more trustworthy than those of valency angle. The latter rest largely on the determination of dipole moments, and, in illustration of the uncertainty which attends their application, it may be noted that furan rings are stable, but that the most recent value assigned to the oxygen valency angle is very much higher than 108° (Hampson, Faraday Society Discussion, April 1934, gives 124—132° for the oxygen angle in diphenyl ethers).

The examination of reduced heterocyclic rings such as those of dioxan, morpholine, etc., is complicated by the possibility of readily interconvertible, strainless forms, but a considerable simplification is introduced by the presence of benzene nuclei fused to the heterocyclic system. In a compound of the general formula (I), in which A and B are the same element, or are different, there is every reason to believe that the four lines joining the centres of A and B to the centres of the carbon atoms to which A and B are attached will pass through the centre of X or of Y. This condition can be fulfilled even if the plane XAB is inclined, about the axis AB, to the plane YAB, as Bennett and Glasstone (this vol., p. 128), in amplifying a suggestion made by Bergmann and Tschudnowsky (*Ber.*, 1932, **65**, 457), have shown it to be in the case of thianthren (A= B = S). The folded structure of thianthren would have certain stereochemical consequences, which have been discussed and investigated by Baw, Bennett, and Dearns (this vol., p. 680), although so far no evidence has been obtained that the folded thianthren structure is stereochemically stable.

(I.)





(II.)

When A and B are not identical, it is still possible for XAB and YAB to be planes, and for these to be inclined to each other, but it seems probable that when the atomic radii of A and B are markedly different, the stability of folded structures would be greater, since, during a theoretical folding process, the valency angles of A and B will change at different rates, and within different limits. Calculation shows, for example, that when A is an oxygen atom (radius, 0·66 Å.) and B is a tervalent arsenic atom (radius, 1·21 Å.), the following relation exists between the oxygen and arsenic valency angles (θ and ϕ, respectively), and the angle ψ between the planes XAB and YAB. Effects of the type discussed by Mills and Nixon (J., 1930, 2510), and effects which might be due to the relative proximity of the oxygen and arsenic atoms are not taken into account :

θ	90°	110°	128°	137·5°
ϕ	72·5°	86·5°	97·5°	103°
ψ	99°	123°	149·5°	180°

The most probable configuration of such a system would appear to be one in which ψ was between 150° and 180°, and if a folded structure were most favourable to the natural angles of both the oxygen and the arsenic atom, it should possess considerable rigidity. A convenient measure of the rigidity would be the angle 180° − ψ.

We have prepared 10-*methylphenoxarsine*-2-*carboxylic acid* (II). If (*a*) the molecule is folded, and if, as a consequence of the dissimilar sizes of the oxygen and the arsenic atom, the folded structure is stable, this acid should exhibit optical activity, irrespective of the disposition of the methyl radical. If (*b*) the molecule is planar as regards X, A, B, and Y, but the methyl radical can lie stably either above or below the plane XABY, optical activity could again result. In view of the fact that arsine has a much smaller dipole moment than ammonia, and of repeated failures on the part of numerous investigators to resolve substituted ammonias, it is at least unlikely that the second configuration (*b*) would lead to molecular dissymmetry of any stability.

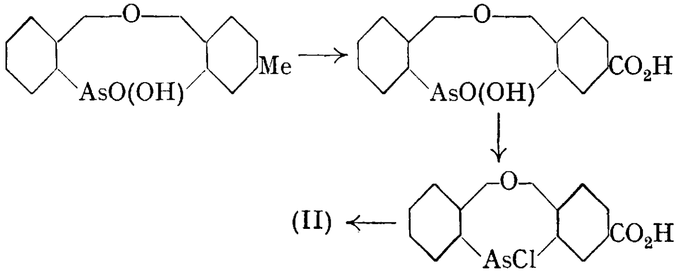
In fact, we have succeeded in resolving 10-methylphenoxarsine-2-carboxylic acid. When a boiling alcoholic solution of the acid (1 mol.) and strychnine (0·25 mol.) was cooled, a strongly dextrorotatory salt separated, from which it became manifest that resolution was probably being effected. Fractional addition of strychnine, followed by systematic crystallisation of successive crops, led to the isolation of three main crops: (1) *Strychnine* d-10-*methylphenoxarsine*-2-*carboxylate*, a sparingly soluble salt having $[\alpha]_{5791}^{20^\circ}$ $+33{\cdot}7^\circ$ and $[\alpha]_{5461}^{20^\circ}$ $+39{\cdot}1^\circ$ (in chloroform), (2) the dl-*salt*, less sparingly soluble than the *d*-salt, and having $[\alpha]_{5791}^{20^\circ}$ $-18{\cdot}2^\circ$ and $[\alpha]_{5461}^{20^\circ}$ $-21{\cdot}1^\circ$, and (3) the l-*salt*, a very soluble salt having $[\alpha]_{5791}^{20^\circ}$ $-51{\cdot}7^\circ$ and $[\alpha]_{5461}^{20^\circ}$ $-60{\cdot}6^\circ$. Removal of the strychnine from these three salts gave three acids having the following properties (rotations in 99·5% alcohol):

	M. p.	$[\alpha]_{5791}^{20^\circ}$.	$[\alpha]_{5461}^{20^\circ}$.
d-*Acid*	135—136°	$+95{\cdot}8^\circ$	$+111{\cdot}5^\circ$
dl-*Acid*	202—203	0	0
l-*Acid*	135—136	$-96{\cdot}0$	$-111{\cdot}7$

The *dl*-acid was prepared according to the following scheme:

$o\text{-}NO_2{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4Me(p) \longrightarrow NH_2{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4Me \longrightarrow$

$AsO_3H_2{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4Me \longrightarrow$



It was observed during the resolution experiments that the active acids could be dissolved in boiling alcohol without racemisation, and it was later found that an alcoholic solution of a pure active acid underwent no loss in activity during several hours' heating under pressure at 100°. We have attempted to determine the speed of racemisation in various solvents, and the energy of activation of the racemisation process, but the acid is so optically stable that so far this has been impossible; *e.g.*, a solution of the *l*-acid in benzyl alcohol retained 95% of its optical activity after being kept at 200° for 2 hours, after which, darkening of the solution prevented further observations being made.

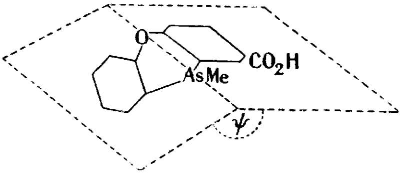
In *N*-sodium hydroxide solution, the *l*-acid had a much higher rotation than in alcoholic solution, and 6 hours' heating of the former solution at 100° caused no measurable racemisation. The total crude acid liberated at the end of this experiment had $[\alpha]_{5791}^{20^\circ}$ $-94{\cdot}2^\circ$ and $[\alpha]_{5461}^{20^\circ}$ $-108{\cdot}6^\circ$. The rate of racemisation in boiling quinoline could not be determined, because of darkening during the first hour's boiling.

When a solution of the *l*-acid in alcohol containing methyl iodide was kept, the *l*-rotation decreased slowly during the first 2 hours, and then began to fall rapidly, the solution becoming inactive in 6 hours. The combination of the acid with methyl iodide appears to be catalysed by the methiodide or by its ions; the combination in aqueous-alcoholic solution in presence of sodium iodide was very much slower than that in alcohol in absence of sodium iodide, and although the two experiments are not strictly comparable, they suggest that the iodide ion is not the effective catalyst.

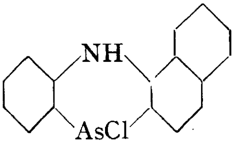
When a solution of the *l*-acid in ethyl alcohol containing ethyl iodide was kept, the *l*-rotation decreased much more slowly than with methyl iodide, as would be expected from the relative reactivity of the two iodides. The solution became completely inactive in about 15 hours.

It is known that addition reactions between tertiary arsines and alkyl iodides are occasionally followed by group displacement (Burrows and Turner, J., 1921, **119**, 426). It is also true that, so far, no arsonium salt has been obtained in an optically stable condition. Yet if the optical activity of the acid is due to the presence of an asymmetric tervalent arsenic atom *of a particularly stable type,* it seems unlikely that the addition of ethyl iodide to the active acid would be accompanied by complete loss of activity, since an asymmetric arsonium ion is produced. The methiodide of the acid should be inactive if the original activity were due to the arsenic dissymmetry. On the other hand, since the formation of an alkiodide is accompanied by the acquisition of a positive charge by the arsenic atom, the effective size of the latter must undergo instantaneous diminution, the arsenic atom in the positive arsonium ion probably being little larger than an oxygen atom. It is almost inconceivable that a folded molecule could withstand the accompanying agitation without complete loss of activity.

At the moment, therefore, we are inclined to favour the folded structure (III) rather than the " asymmetric arsenic atom " as the cause of the activity of 10-methylphenoxarsine-2-carboxylic acid. For several years, experiments have been in progress on the resolution of a simple tertiary arsine derivative, and clearly this matter and the resolution of the above meth- and eth-iodide will require attention. Work is also in progress on the attempted resolution of derivatives of phenoxthionine (I; A = O; B = S), phenoxtellurine (I; A = O; B = Te), and similar compounds, in which the complication arising from the attachment of a group to B is absent.



(III.)



(IV.)

During the course of the present work, Allen, Wells, and Wilson (*J. Amer. Chem. Soc.*, 1934, **56**, 233) claimed to have obtained evidence in favour of an " asymmetric arsenic atom." They treated the chlorobenzophenarsazine (IV) with silver *d*-bromocamphorsulphonate, and obtained two substances which they regarded as (IV) in which the chlorine atom is replaced by the bromocamphorsulphonate group. The combined yield of the two substances was less than 10% of that theoretically possible, and the calculated " specific rotations of the arsenic radicals " given for the two substances as − 24·9° and + 25·6° are based on two mean polarimetric readings of the order of 0·1°. In view of the unavoidable experimental error, and of the uncertainty as to the constitution of a substance containing a sulphonic acid group in attachment to a tervalent arsenic atom in a phenarsazine, it is impossible at the moment to assess the significance of the work of the above authors. If the two substances which they isolated have the constitutions and the rotations assigned to them, it appears probable that they are stereoisomeric forms due to a folded phenarsazine structure.

EXPERIMENTAL.

o-*Nitrophenyl* p-*Tolyl Ether.*—This substance was obtained by the method described by Henley (J., 1930, 1222) in almost 100% crude yield (pure material over 75%).

o-*Aminophenyl* p-*Tolyl Ether.*—The nitro-compound was reduced with iron filings, water, and a little acetic acid at 100°. The reduction mixture was extracted with hot alcohol, and the filtered extract freed from the bulk of the alcohol by distillation. The residue was poured into excess of diluted hydrochloric acid (1 : 1). When the resulting paste was cold, it was filtered off, and the hydrochloride was dried at 100° (yield, 85%). The base obtained from the salt had b. p. 178°/10 mm. or 183°/12 mm. (compare Cook and Hiller, *Amer. Chem. J.*, 1900, **24**, 529).

2-p-*Tolyloxyphenylarsonic Acid.*—The foregoing hydrochloride (129 g.) was sieved and mixed with 110 c.c. of concentrated hydrochloric acid and 150 g. of crushed ice. A solution of 39 g. of sodium nitrite in 110 c.c. of water was stirred in rapidly under the surface. A trace of insoluble material was filtered off, and the solution was then neutralised with sodium hydrogen carbonate in presence of ice. The diazo-solution was added rapidly under the surface of a vigorously stirred solution containing 112 g. of arsenious oxide, 235 g. of anhydrous sodium carbonate and 900 c.c. of water, initially at 50—60°. Dilute copper sulphate solution was added at intervals. After the addition, stirring was continued until no diazo-compound remained in solution. The whole was cooled, the semi-solid tar squeezed, and the liquid filtered and acidified with hydrochloric acid. The arsonic acid which separated was dissolved in boiling alcohol, the solution was filtered, and then treated with about 3 vols. of boiling water. On cooling, the arsonic *acid* separated as short, rectangular prisms, m. p. 192—193°. The yield was variable (20—40%) (Found: C, 50·3; H, 4·45. $C_{13}H_{13}O_4As$ requires C, 50·6; H, 4·25%).

2-*Methylphenoxarsinic Acid.*—Roberts and Turner (J., 1925, **127**, 2004) found that *o*-phenoxyphenylarsonic acid underwent sulphonation when an attempt was made to convert it into phenoxarsinic acid by means of concentrated sulphuric acid. The tolyloxy-acid tends to sulphonate, but ring closure was effected readily as follows: The tolyloxyarsonic acid (30 g.) was slowly added to 150 g. of ice-cold, well-stirred concentrated sulphuric acid. When the addition was complete, the mixture was heated to 100°, and kept at 100° for 5 minutes, then cooled and poured on ice. The solid was collected, washed with water, and dissolved in the minimum of boiling alcohol. The filtered solution was treated with about 10 vols. of boiling water, and allowed to cool to 0°. The pure *acid* (yield, 70%) forms hexagonal plates or spherical aggregates, m. p. 245—246° (corr.) (Found: As, 26·4. $C_{13}H_{11}O_3As$ requires As, 25·8%).

2-*Carboxyphenoxarsinic Acid.*—A solution containing the foregoing acid (11·6 g.; 1 mol.), 2·4 g. (0·5 mol.) of sodium carbonate, and 80 c.c. of water was boiled, and to it was added, in about ten portions, during 15 minutes, a boiling solution of 12·8 g. (2 mols.) of potassium permanganate in 400 c.c. of water. Boiling was continued for a further 10 minutes, and a rapid current of sulphur dioxide was passed through the suspension until only a faint pink colour persisted (5 minutes). The cooled suspension was filtered, and the solid was ground with aqueous ammonia. The resulting suspension was filtered. Acidification of the filtrate with hydrochloric acid gave crude 2-*carboxyphenoxarsinic acid.* This was dissolved in boiling alcohol, and the solution was filtered and treated with boiling water (1 vol.). After cooling to 0°, the acid (yield, 64%) was obtained as striated needles, m. p. 280—281° (corr.) (efferv.) (Found; C, 46·0; H, 3·5; As, 22·1; loss at 150—160°, 5·4. $C_{13}H_9O_5As,H_2O$ requires C, 46·2; H, 3·25; As, 22·2; H_2O, 5·3%). Oxidation in the cold, using the same materials, was very slow (2—3 days), and gave an inferior yield (45%).

10-*Chlorophenoxarsine*-2-*carboxylic Acid.*—The preceding acid was ground to a thin cream with concentrated hydrochloric acid, chloroform, containing a little iodine, was added, and the warm suspension was saturated with sulphur dioxide until the colour of the iodine had disappeared. The suspension was then cooled and filtered. The *chloro*-compound was washed with water, and dried in a vacuum. It crystallised from absolute alcohol, containing a little concentrated hydrochloric acid, in needles, m. p. 280—281° (corr.) (Found: Cl, 10·9. $C_{13}H_8O_3ClAs$ requires Cl, 11·0%). Occasionally, the original mixture of carboxyphenoxarsinic acid and concentrated hydrochloric acid set to a mass of needles, presumably of an oxychloride.

dl-10-*Methylphenoxarsine*-2-*carboxylic Acid.*—The crude, dry chloro-carboxylic acid (32 g.; 1 mol.) was gradually added to an ethereal solution containing 4 mols. of methylmagnesium iodide. Each portion reacted vigorously. The clear solution was gently boiled during 2 hours, and then decomposed with ice and dilute hydrochloric acid. The aqueous layer was extracted with ether, which was combined with the original ethereal layer. The ethereal solution was washed with water, and extracted twice with aqueous ammonia. The ammonia solution was acidified, and the precipitated acid collected and dried at 100°. It crystallised from absolute alcohol in clusters of small needles, m. p. 202—203° (corr.) (Found: C, 55·4; H, 3·7; As, 24·9. $C_{14}H_{11}O_3As$ requires C, 55·6; H, 3·7; As, 24·8%).

The *methiodide* was readily formed when the acid was heated at 100° with absolute ethyl alcohol and methyl iodide. It forms elongated plates, m. p. 250° (efferv.), and is very sparingly soluble in alcohol. It could not be crystallised from an organic solvent, and from water it forms the *hydrate*, rectangular needles, m. p. *ca.* 250° (decomp.) (Found: I, 27·7. $C_{15}H_{14}O_3AsI,H_2O$ requires I, 27·5%).

Resolution of dl-10-*Methylphenoxarsine*-2-*carboxylic Acid.*—To a boiling solution of 65·4 g. of the *dl*-acid in 2 l. of boiling 99·5% ethyl alcohol were added 18·1 g. of strychnine (0·25 mol.).

The solution was left over-night in the ice-chest, and gave 8·0 g. of salt *A*, having $[\alpha]^{20^\circ}_{5791}$ + 21·2°, in chloroform. To the mother-liquor from *A* were added, at the b. p., another 18·1 g. of strychnine. On being kept in the ice-chest as before, 48 g. of salt *B* separated, having $[\alpha]^{20^\circ}_{5791}$ + 23·8°. Addition of 18·1 g. of strychnine to the mother-liquor from *B* gave 15 g. of a salt *C*, having $[\alpha]^{20^\circ}_{5791}$ + 7·2°.

The remaining 18·1 g. of strychnine were added to the mother-liquor from *C*, and 24 g. of a salt *D* were obtained having $[\alpha]^{20^\circ}_{5791}$ − 12·8°. Successive evaporation of the mother-liquor from *D* gave the following salts: 11·2 g. of *E*, with $[\alpha]^{20^\circ}_{5791}$ − 26·2°; 6·1 g. of *F*, with $[\alpha]^{20^\circ}_{5791}$ − 46·5°; and 3·3 g. of *G*, with $[\alpha]^{20^\circ}_{5791}$ − 53·5°. Further evaporation of the mother-liquor gave a very small quantity of salt only.

Salts *A* and *B* were combined, and recrystallised (8 times) from alcohol until the specific rotation no longer changed, when 10·5 g. of pure strychnine *d*-salt were obtained. Recrystallisation of *C* also gave more strychnine *d*-salt.

Concentration of the mother-liquors from the base *d*-acid crops gave mostly strychnine *dl*-salt, contaminated with base *d*-salt, the rotations of crops varying from $[\alpha]^{20^\circ}_{5791}$ + 26·6° to − 15·3°. By recrystallising crops *C* to *G*, the less soluble partial racemate separated first, and, on concentrating the mother-liquor, a purer strychnine *l*-acid salt was obtained. This was repeated many times until the optically pure *l*-acid salt (23·7 g.) was obtained.

Strychnine d-10-*methylphenoxarsine*-2-*carboxylate* crystallises from ethyl alcohol in prismatic needles, and has $[\alpha]^{20^\circ}_{5791}$ + 33·7° and $[\alpha]^{20^\circ}_{5461}$ + 39·1° (c = 2·0705; l = 2; $\alpha^{20^\circ}_{5791}$ = + 1·395°; $\alpha^{20^\circ}_{5461}$ = + 1·62°) in chloroform (Found: C, 65·7; H, 5·4. $C_{35}H_{33}O_5N_2As$ requires C, 66·0; H, 5·2%).

Strychnine dl-10-*methylphenoxarsine*-2-*carboxylate* crystallises from ethyl alcohol in plates; $[\alpha]^{20^\circ}_{5791}$ − 18·2° and $[\alpha]^{20^\circ}_{5461}$ − 21·1°, in chloroform (c = 1·591; l = 2; $\alpha^{20^\circ}_{5791}$ = − 0·58°; $\alpha^{20^\circ}_{5461}$ = − 0·67°) (Found: C, 65·7; H, 5·3%).

Strychnine l-10-*methylphenoxarsine*-2-*carboxylate* crystallises from alcohol in slender needles; $[\alpha]^{20^\circ}_{5791}$ − 51·7° and $[\alpha]^{20^\circ}_{5461}$ − 60·6°, in chloroform (c = 2·029; l = 2; $\alpha^{20^\circ}_{5791}$ = − 2·10°; $\alpha^{20^\circ}_{5461}$ = − 2·46°) (Found: C, 65·7; H, 5·3%).

Decomposition of the strychnine salts was effected in the usual manner with ammonia. Acidification of the ammoniacal solution gave the free acids.

d-10-*Methylphenoxarsine*-2-*carboxylic acid* crystallises from aqueous alcohol in hair-like needles, m. p. 135—136° (corr.); $[\alpha]^{20^\circ}_{5791}$ + 95·8°, $[\alpha]^{20^\circ}_{5461}$ + 111·5°, in 99·5% ethyl alcohol (c = 1·659; l = 2; $\alpha^{20^\circ}_{5791}$ = + 3·18°; $\alpha^{20^\circ}_{5461}$ = + 3·70°). It is very readily soluble in alcohol (Found: C, 55·6; H, 3·9. $C_{14}H_{11}O_3As$ requires C, 55·6; H, 3·7%). The l-*acid* crystallises from aqueous alcohol in hair-like needles, m. p. 135—136° (corr.); $[\alpha]^{20^\circ}_{5791}$ − 96·0°, $[\alpha]^{20^\circ}_{5461}$ − 111·7°, in 99·5% ethyl alcohol (c = 1·052; l = 2; $\alpha^{20^\circ}_{5791}$ = − 2·02°; $\alpha^{20^\circ}_{5461}$ = − 2·35°) (Found: C, 55·7; H, 3·8%).

Action of Heat on l-*Acid in Benzyl-alcoholic Solution.*—0·2916 G. of pure *l*-acid was dissolved in benzyl alcohol, and the solution made up to 20 c.c. It had $[\alpha]^{20^\circ}_{5791}$ − 57·6° and $[\alpha]^{20^\circ}_{5461}$ − 67·9° (c = 1·458; l = 2; $\alpha^{20^\circ}_{5791}$ = − 1·68°; $\alpha^{20^\circ}_{5461}$ = − 1·98°). After 2 hours' heating at 200°, it had $[\alpha]^{20^\circ}_{5791}$ − 54·9°, $[\alpha]^{20^\circ}_{5461}$ − 64·8° ($\alpha^{20^\circ}_{5791}$ = − 1·60°; $\alpha^{20^\circ}_{5461}$ = − 1·89°).

Action of Methyl Iodide in Alcoholic Solution on the l-*Acid.*—0·1992 G. of pure *l*-acid was dissolved in ethyl alcohol, 5 c.c. of methyl iodide were added, and the solution was made up to 20 c.c. The following observations were made (l = 2):

Time, mins.	0	35	65	105	165	330	375
α_{5791}	−1·63°	−1·63°	−1·59°	−1·48°	−1·06°	−0·31°	−0·04°
α_{5461}	−1·89	−1·87	−1·84	−1·70	−1·21	−0·39	−0·05

Action of Ethyl Iodide in Ethyl-alcoholic Solution on the l-*Acid.*—A precisely similar experiment with 0·2304 g. of the *l*-acid and ethyl iodide gave:

Time, mins.	0	60	150	230	435	1000
α_{5791}	−1·98°	−1·98°	−1·94°	−1·94°	−1·32°	0°
α_{5461}	−2·29	−2·29	−2·26	−2·26	−1·51	0

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