226. *The Configuration of Heterocyclic Compounds. Part X. The Optical Resolution of* 10-*Phenylphenoxarsine*-10-*oxide*-2-*carboxylic Acid.*

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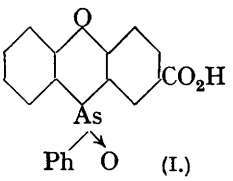
The resolution of 10-phenylphenoxarsine-10-oxide-2-carboxylic acid is described. The optically active acids obtained had $[\alpha]_{5791}^{20°}$ +36·4° and −29·7° in dilute aqueous ammonia. The active ammonium salt racemises slowly at 20°, and at 80° it has a half-life period of 6·4 minutes. Reduction to the parent phenylphenoxarsine acid was accompanied by complete loss of activity.

IT was found by Lesslie and Turner (J., 1936, 730) that oxidation of *l*-10-phenylphenoxarsine-2-carboxylic acid was accompanied by complete loss of activity and it was therefore necessary to attempt the resolution of 10-phenylphenoxarsine-10-oxide-2-carboxylic acid for comparison with the parent phenylphenoxarsine acid.

Several attempts have been made to demonstrate the molecular dissymmetry of arsenic oxides, but no positive result has hitherto been recorded (Burrows and Turner, J., 1921,

119, 426; Aeschlimann and McCleland, J., 1924, **125**, 2025; Aeschlimann, J., 1925, **127**, 811).

10-Phenylphenoxarsine-10-oxide-2-carboxylic acid (I) presents two possible sources of dissymmetry. It contains an asymmetric "quinque"-valent arsenic atom and in addition, if the molecule is possessed of a "folded" configuration, dissymmetry would again result. It was considered probable, however, that in the above oxide, owing to the similarity in size between the positively charged arsenic and the oxygen atom, the stability of such a folded configuration might be so decreased that optical activity dependent on it would not occur.



(I.)

The non-resolution of certain phenoxarsonium salts was ascribed by Lesslie and Turner to a similar instability in the folded configuration of the molecule (J., 1935, 1051).

The above phenylphenoxarsine-oxide acid was found to be rather a weak acid and some difficulty was experienced in finding a salt suitable for resolution experiments. The quinidine and strychnine salts were examined, but during recrystallisation from various solvents there was a strong tendency for free acid to separate, and decomposition of several fractions of the salts obtained always gave the optically inactive acid. The cinchonidine salt was also prepared, but it remained as an oil. A number of fractions of oil were obtained by fractional precipitation with water from the ethyl-alcoholic solution and the acids obtained by the decomposition of these several fractions were found to be strongly optically active.

The resolution was eventually achieved through the morphine salt. To a hot ethyl-alcoholic solution of the acid and its equivalent of morphine, ether was added and successive crops were obtained whose specific rotation in methyl alcohol varied from −66·7° to +17·9°. It was soon apparent that certain fractions consisted mainly of morphine salt and others were either free acid or free base. They were easily distinguished from each other by their relative solubility in methyl alcohol, the acid being the most sparingly soluble.

The salts could be recrystallised from methyl alcohol–ether without change in composition, whereas, from ethyl alcohol–ether, there was a tendency for free acid to separate.

The highest value obtained for the specific rotation of *morphine* l-10-*phenylphenoxarsine*-10-*oxide*-2-*carboxylate* was $[\alpha]_{5791}^{20°}$ −88·7° in methyl alcohol. The alcoholic solution underwent mutarotation slowly at the ordinary temperature until the rotation was −57·0°; thereafter, no further change was observed. Experiments were carried out to determine the velocity constant for the racemisation of the above *l*-acid salt in methyl alcohol at 80° and at 100°, but the racemisation process was too slow for accurate determinations to be made. Heating its methyl-alcoholic solution in a sealed tube for 1½ hours at 100° effected complete racemisation of the salt.

The lowest value obtained for the rotation of the d-*acid* salt was $[\alpha]_{5791}^{20°}$ −35·3° in methyl alcohol. Recrystallisation raised the value of its rotation to that of either the partial racemate ($[\alpha]_{5791}^{20°}$ −57·0° approx.) or the *l*-acid salt. It was possible by varying the conditions of crystallisation to effect an asymmetric transformation of Kuhn's "second order" and obtain only one of the diastereoisomeric salts, *viz.*, that of the *l*-acid salt (*Ber.*, 1932, **65**, 49). When crystallisation from methyl alcohol–ether took place at 0°, the salt which separated had approximately $[\alpha]_{5791}^{20°}$ −88°, and when the crystallisation occurred more slowly at the ordinary temperature, the salt which separated was contaminated with racemate. The *d*-acid salt was obtained by concentrating under diminished pressure the mother-liquor from the *l*-acid salt and adding ether to the residual alcoholic solution.

The salts were decomposed by adding ice-cold dilute hydrochloric acid to a suspension of the salt in methyl alcohol. The acid was purified by dissolving it in ice-cold, dilute aqueous ammonia and precipitating the acid by addition of ice-cold, dilute hydrochloric acid. The active acids were very sparingly soluble in most organic solvents, and their rotation was most conveniently measured in dilute ammonia solution.

The highest value obtained for the rotation of the *l*-acid from the morphine salt was $[\alpha]_{5791}^{20°}$ −11·7°, in dilute aqueous ammonia, and for the *d*-acid, $[\alpha]_{5791}^{20°}$ +4·0°.

During the resolution, two fractions of free acid separated, one having $[\alpha]_{5791}^{20°}$ +33·1°, and the other having $[\alpha]_{5791}^{20°}$ −29·7° in dilute aqueous ammonia. Purification through the ammonium salt raised the rotation of the *d*-acid to +36·4°, but the rotation of the *l*-acid remained approximately the same. The ammoniacal solutions underwent mutarotation slowly at the ordinary temperature.

The half-life period of the active ammonium salt at 80° was 6·4 minutes, and at 50° it was 35 minutes.

Reduction of the active oxide acid gave 10-phenylphenoxarsine-2-carboxylic acid, which was optically inactive.

During the resolution, there was no evidence whatever of the oxide acid undergoing reduction to the parent phenylphenoxarsine acid, as was observed in the attempted resolution of the corresponding phenoxselenine-oxide acid by Thompson and Turner (J., 1938, 29).

The instability of this phenylphenoxarsine-oxide acid is in contrast to the high optical stability shown by *p*-carboxyphenylmethylethylarsine sulphide, resolved by Mills and Raper (J., 1925, **127**, 2479), and it may be associated with the ready hydration of arsine oxides to arsine dihydroxides.

Attempts to prepare 10-phenylphenoxarsine-10-sulphide-2-carboxylic acid were unsuccessful and always resulted in the production of the 10-phenylphenoxarsine acid only.

Experimental.

For the purification of large quantities of 10-phenylphenoxarsine-10-oxide-2-carboxylic acid, dilute acetic acid is a more convenient solvent than the dilute alcohol recommended by Lesslie and Turner (J., 1936, 730).

Resolution.—15 G. of the *dl*-acid and 11·9 g. of morphine (1 mol.) were dissolved in 1150 c.c. of ethyl alcohol. To the hot filtered solution, ether (2 l.) was added, and the solution allowed to cool to the ordinary temperature. 10·2 G. of salt *A* were deposited having $[\alpha]_{5791}^{20°}$ −66·7° in methyl alcohol ($l = 2$; $c = 0·562$; $\alpha_{5791}^{20°} = -0·75°$). (Owing to the sparing solubility of the salts, it was necessary to heat in order to effect their complete solution in methyl alcohol.) Most of the ether was removed by distillation from the mother-liquor from *A*, and a second crop separated, *B* (1·9 g.), which had $[\alpha]_{5791}^{20°}$ +17·9° in methyl alcohol ($l = 2$; $c = 0·392$; $\alpha_{5791}^{20°} = +0·14°$). This fraction was much more sparingly soluble in methyl alcohol than *A* and it was later found to be free acid. The mother-liquor from *B* was concentrated under diminished pressure until only about half of the alcohol remained. Ether was then added to the residual solution and 3 g. of salt *C* were obtained which had $[\alpha]_{5791}^{20°}$ −76·7° ($l = 2$; $c = 0·6195$; $\alpha_{5791}^{20°} = -0·95°$). Similar treatment of the mother-liquor from *C* (*viz.*, concentration of the alcoholic solution under diminished pressure and subsequent addition of ether) was repeated and a series of crops were obtained; *D* (2 g.) with $[\alpha]_{5791}^{20°}$ −41·6°; *E* (1·6 g.) with $[\alpha]_{5791}^{20°}$ −41·2°. These two salts were more soluble than the preceding crops and mutarotation was first observed in their methyl-alcoholic solutions. Treatment of the mother-liquor from *E* gave 3·7 g. of a substance, which was readily soluble in cold methyl alcohol and had $[\alpha]_{5791}^{20°}$ −104·7°. This was free base.

Salt *A* was treated with 300 c.c. of boiling methyl alcohol. The suspension was kept at the b. p. for a few minutes and filtered hot. 3·4 G. of salt remained undissolved and had $[\alpha]_{5791}^{20°}$ −86·9° in methyl alcohol ($l = 2$; $c = 0·512$; $\alpha_{5791}^{20°} = -0·89°$). After 20 hours at the ordinary temperature, the rotation of this solution had fallen to $[\alpha]_{5791}^{20°}$ −66·4° ($\alpha_{5791}^{20°} = -0·68°$). After a second similar extraction of the above salt, 2·1 g. of salt were obtained with $[\alpha]_{5791}^{20°}$ −87·3°. Ether was added to the hot filtrate and the solution was put in the ice-chest; 0·6 g. of salt was obtained, having $[\alpha]_{5791}^{20°}$ −88·5° ($l = 2$; $c = 0·61$; $\alpha_{5791}^{20°} = -1·08°$).

To the first methyl-alcoholic extract, ether was added, and the solution kept at the ordinary temperature. 4·9 G. of salt separated which had $[\alpha]_{5791}^{20°}$ −58·2° in methyl alcohol. An extraction of this salt was carried out as above but with ethyl alcohol; 0·85 g. of salt remained undissolved and it had $[\alpha]_{5791}^{20°}$ −76·6° in methyl alcohol. On addition of ether to the ethyl-alcoholic solution, 1·25 g. of solid were obtained which was very sparingly soluble in methyl alcohol. It had $[\alpha]_{5791}^{20°}$ −28·0° in methyl alcohol ($l = 2$; $c = 0·268$; $\alpha_{5791}^{20°} = -0·15°$) and was found to be free acid. It was dissolved in ice-cold, dilute aqueous ammonia, and the acid precipitated with ice-cold dilute hydrochloric acid. The acid then had $[\alpha]_{5791}^{20°}$ −29·7° in dilute aqueous ammonia ($l = 2$; $c = 0·69$; $\alpha_{5791}^{20°} = -0·41°$). Further purification through the ammonium salt did not raise the specific rotation.

Substance *B* dissolved readily in dilute aqueous ammonia, the solution having $[\alpha]_{5791}^{20°}$ +33·1° ($l = 2$; $c = 0{\cdot}559$; $\alpha_{5791}^{20°} = +0{\cdot}37°$). The solution underwent mutarotation at the ordinary temperature and the final observed angle was −0·09°, indicating that a little morphine was present. This fraction was therefore dissolved in dilute aqueous ammonia, cooled to −10°, and the filtered ammoniacal solution acidified with dilute hydrochloric acid, also cooled to −10°. The resulting acid was filtered off, dried, and its rotation measured in ammoniacal solution. (Only the amount of dilute aqueous ammonia necessary to effect solution was added to the aqueous suspension of the acid.) It had $[\alpha]_{5791}^{20°}$ +36·4° ($l = 2$; $c = 0{\cdot}57$; $\alpha_{5791}^{20°} = +0{\cdot}56°$).

Salt *C* was recrystallised from methyl alcohol–ether and cooled quickly at 0°; 1·5 g. of salt were obtained, having $[\alpha]_{5791}^{20°}$ −84·5° in methyl alcohol. After 16 hours (at room temperature) the rotation had fallen to $[\alpha]_{5791}^{20°}$ −67·2°.

Salts *D* and *E* were combined and recrystallised from methyl alcohol–ether and cooled to the ordinary temperature; 1·4 g. of salt were obtained having $[\alpha]_{5791}^{20°}$ −57·0° ($l = 2$; $c = 0{\cdot}509$; $\alpha_{5791}^{20°} = -0{\cdot}58°$). After extraction with boiling methyl alcohol, the salt had $[\alpha]_{5791}^{20°}$ −53·8°. Decomposition of this fraction gave the racemic acid. The mother-liquor from the above crystallisation was concentrated under diminished pressure, and ether added to the residual alcoholic solution; 0·7 g. of salt was obtained having $[\alpha]_{5791}^{20°}$ −35·3° in methyl alcohol ($l = 2$; $c = 0{\cdot}623$; $\alpha_{5791}^{20°} = -0{\cdot}44°$).

The mother-liquors from all the extractions and crystallisations were combined, and all the solvent removed by distillation. The residue was extracted with boiling methyl alcohol as before; 0·5 g. of salt remained undissolved and had $[\alpha]_{5791}^{20°}$ −86·3°. To the hot methyl-alcoholic extract, ether was added, and the solution cooled quickly to 0°; 0·7 g. of salt separated having $[\alpha]_{5791}^{20°}$ −81·0° in methyl alcohol.

Morphine l-10-*phenylphenoxarsine*-10-*oxide*-2-*carboxylate* crystallised from methyl alcohol–ether in spherical aggregates of rhombic crystals, m. p. 245—246° (decomp.). It had $[\alpha]_{5791}^{20°}$ −88·5° and $[\alpha]_{5461}^{20°}$ −101·6° in methyl alcohol ($l = 2$; $c = 0{\cdot}61$; $\alpha_{5791}^{20°} = -1{\cdot}08°$; $\alpha_{5461}^{20°} = -1{\cdot}24°$). Further crystallisation did not raise the rotation (Found: C, 65·1; H, 5·1. $C_{19}H_{13}O_4As,C_{17}H_{19}O_3N$ requires C, 65·0; H, 4·9%).

Morphine d-10-*phenylphenoxarsine*-10-*oxide*-2-*carboxylate* separated from methyl alcohol–ether in small plates, m. p. 241—243° (decomp.) with slight previous softening. It had $[\alpha]_{5791}^{20°}$ −35·3° and $[\alpha]_{5461}^{20°}$ −38·5° in methyl alcohol ($l = 2$; $c = 0{\cdot}623$; $\alpha_{5791}^{20°} = -0{\cdot}44°$; $\alpha_{5461}^{20°} = -0{\cdot}48°$). Recrystallisation converted it either into the partially racemic salt or into the *l*-acid salt (Found: C, 63·3; H, 4·6. $C_{19}H_{13}O_4As,C_{17}H_{19}O_3N,H_2O$ requires C, 63·3; H, 5·0%).

The diastereoisomeric salts racemised very slowly at the ordinary temperature. The rotation of a methyl-alcoholic solution of the *l*-acid salt, initially $[\alpha]_{5791}^{20°}$ −87·3° ($\alpha_{5791}^{20°} = -1{\cdot}06°$), had changed to $[\alpha]_{5791}^{20°}$ −57·7° ($\alpha_{5791}^{20°} = -0{\cdot}70°$) after 24 hours at 20°. In another experiment, a methyl-alcoholic solution of the *l*-acid salt, having $[\alpha]_{5791}^{20°}$ −86·3° ($\alpha_{5791}^{20°} = -1{\cdot}02°$), was heated in a sealed tube at 100° for 1½ hours. The rotation was then $[\alpha]_{5791}^{20°}$ −57·5° ($\alpha_{5791}^{20°} = -0{\cdot}68°$). Again, a methyl-alcoholic solution of the *d*-acid salt, with an initial rotation $[\alpha]_{5791}^{20°}$ −41·2° ($\alpha_{5791}^{20°} = -0{\cdot}70°$), underwent mutarotation and after standing at 19° for 2 days had $[\alpha]_{5791}^{20°}$ −62·4° ($\alpha_{5791}^{20°} = -1{\cdot}06°$).

Decomposition of the purest *l*-acid salt obtained gave an active acid which had $[\alpha]_{5791}^{20°}$ −11·7° and $[\alpha]_{5461}^{20°}$ −12·5° in dilute aqueous ammonia ($l = 2$; $c = 0{\cdot}641$; $\alpha_{5791}^{20°} = -0{\cdot}15°$; $\alpha_{5461}^{20°} = -0{\cdot}16°$). The acid obtained from the decomposition of the purest *d*-acid salt had $[\alpha]_{5791}^{20°}$ + 4·0° ($\alpha_{5791}^{20°} = +0{\cdot}05°$).

l-10-*Phenylphenoxarsine*-10-*oxide*-2-*carboxylic acid* melted at 313—315° with slight previous softening. The purest *l*-acid obtained had $[\alpha]_{5791}^{20°}$ −29·7° and $[\alpha]_{5461}^{20°}$ −36·2° in dilute aqueous ammonia ($l = 2$; $c = 0{\cdot}69$; $\alpha_{5791}^{20°} = -0{\cdot}41°$; $\alpha_{5461}^{20°} = -0{\cdot}50°$) (Found: C, 60·1; H, 3·4. $C_{19}H_{13}O_4As$ requires C, 60·0; H, 3·45%).

d-10-*Phenylphenoxarsine*-10-*oxide*-2-*carboxylic acid* melted at 312—314° with slight previous softening. The purest *d*-acid obtained had $[\alpha]_{5791}^{20°}$ +36·4° and $[\alpha]_{5461}^{20°}$ +43·5° in dilute aqueous ammonia ($l = 2$; $c = 0{\cdot}57$; $\alpha_{5791}^{20°} = +0{\cdot}56°$; $\alpha_{5461}^{20°} = +0{\cdot}67°$) (Found: C, 60·1; H, 3·4%).

The active acids racemised very slowly in dilute aqueous ammonia at 20°. The half-life period of the acid was determined at 80° and 50°. An ammoniacal solution of the *d*-acid, which had $\alpha_{5791}^{20°} = +0{\cdot}56°$, was heated in a sealed tube at 80° for 30 minutes; it then had $\alpha_{5791}^{20°} = +0{\cdot}01°$. The value of $1/t \,.\, \log_{10}\alpha_0/\alpha_t$ was 0·047. Similarly, a solution of the *l*-acid, which initially had $\alpha_{5791}^{20°} = -0{\cdot}15°$, after heating for 15 minutes at 80°, had $\alpha_{5791}^{20°} = -0{\cdot}03°$, hence $1/t \,.\, \log_{10}\alpha_0/\alpha_t$ is 0·047; the half-life period of the acid ion at 80° is therefore 6·4 minutes.

The half-life period of the acid in dilute aqueous ammonia was also determined at 50°, and the following observations made :

Time (mins.)	0	10	30	90
$\alpha_{5791}^{20°}$	+0·39°	+0·32°	+0·21°	+0·07°
$1/t \cdot \log_{10} a_0/a_t$	—	0·0086	0·0089	0·0083

The average value for k is therefore 0·0086, hence the half-life period of the acid ion at 50° is 35 minutes.

The acid recovered from all the racemisation experiments melted at 320° and was the racemic oxide acid.

Throughout the resolution there was no trace of the reduced acid; the latter melts at 206—207° and the active reduced acid melts at 189—190°.

Reduction.—0·5 G. of the active oxide acid was suspended in dilute hydrochloric acid, and a little iodine added. Sulphur dioxide was passed through the warmed suspension for 15 minutes. The reduced acid obtained was optically inactive.

The reduction was attempted with sodium hyposulphite. The oxide acid was ground with aqueous sodium hyposulphite solution, but only partial reduction was effected. The reduced acid isolated was optically inactive and the oxide acid recovered was unchanged in its specific rotation.

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