189. *The Configuration of Heterocyclic Compounds. Part IX. The Optical Resolution of 8-Chloro-10-phenylphenoxarsine-2-carboxylic Acid.*

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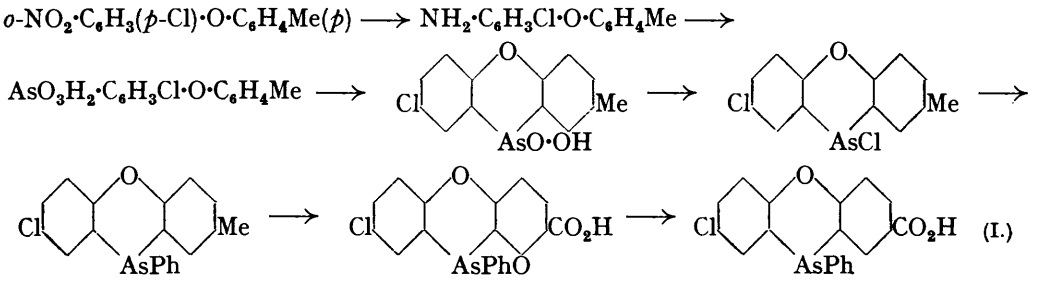
A chloro-substituted 10-phenylphenoxarsine-carboxylic acid has been prepared and resolved. The active acids showed the high optical stability characteristic of this class of compound.

THE resolution of three 10-substituted phenoxarsine-2-carboxylic acids has been described by Lesslie and Turner (J., 1934, 1178; 1935, 1268; 1936, 730) and an important feature of this class of optically active compound was their very high optical stability. It therefore seemed desirable to prepare and attempt the resolution of a more heavily substituted phenoxarsine in order to see if the stability was affected by substitution in the benzene ring. The substance synthesised was dl-8-*chloro*-10-*phenylphenoxarsine*-2-*carboxylic acid* (I):



(I.)

The acid was resolved by means of its *d*- and *l*-α-phenylethylamine salts.

d-α-*Phenylethylamine* l-8-*chloro*-10-*phenylphenoxarsine*-2-*carboxylate* has $[\alpha]_{5791}^{20°}$ — 71·7° and $[\alpha]_{5461}^{20°}$ — 85·4° in methyl alcohol. The l-*base* d-*acid* salt has $[\alpha]_{5791}^{20°}$ + 71·3° and $[\alpha]_{5461}^{20°}$ + 85·0°. The optically pure 8-*chloro*-10-*phenylphenoxarsine*-2-*carboxylic acids*, obtained by decomposition of the α-phenylethylamine salts and subsequent recrystallisation, have $[\alpha]_{5791}^{20°}$ ± 69° and $[\alpha]_{5461}^{20°}$ ± 81·9° in acetone. 10-Phenylphenoxarsine-2-carboxylic acid itself has a much higher specific rotation, *viz.*, ± 223° in ethyl alcohol.

Like the simpler 10-substituted phenoxarsine-2-carboxylic acids, the new acid has high optical stability. An acetone solution of the *l*-acid lost none of its activity when it was heated in a sealed tube for 6 hours at 100°. After the *d*-acid had been boiled for 3 hours with N-sodium hydroxide, the rotation of the recovered acid was unchanged. The sodium salt was so sparingly soluble that its rotation could not be measured.

Experimental.

4-Chloro-2-aminophenyl p-Tolyl Ether.—4-Chloro-2-nitrophenyl *p*-tolyl ether, prepared by Henley's method (J., 1930, 1222), was reduced at 100° with iron filings, water, and a little acetic acid. The base was extracted from the mixture with hot alcohol, precipitated by water, and purified either by conversion into the hydrochloride or by crystallisation from alcohol. It melted at 56—57° (compare Bayer and Co., D.R.-P. 216,642).

5-Chloro-2-p-tolyloxyphenylarsonic Acid.—117 G. of the foregoing base were heated with 125 c.c. of concentrated hydrochloric acid, the mixture cooled, and 100 g. of ice added. A solution of 30 g. of sodium nitrite in 100 c.c. of water was stirred in under the surface and the filtered diazo-solution was added rapidly under the surface of a vigorously stirred solution containing 99 g. of arsenious oxide, 212 g. of anhydrous sodium carbonate, and 800 c.c. of water initially at 65°. Dilute copper sulphate solution was added at intervals. Stirring was continued until no diazo-compound remained in solution. The whole was heated on the water-bath for ½ hour and cooled, and the filtered liquid acidified with hydrochloric acid. The *arsonic acid* (yield, 12%) which separated crystallised from alcohol in long rectangular plates, m. p. 199—200°. Neutralisation of the diazo-solution before addition to the arsenite solution resulted in much smaller yields of arsonic acid (Found: As, 21·9. $C_{13}H_{12}O_4ClAs$ requires As, 21·9%).

8-Chloro-2-methylphenoxarsonic Acid.—30 G. of the preceding arsonic acid were added slowly to 150 g. of ice-cold, well-stirred concentrated sulphuric acid. The temperature was then raised to 100° and maintained for 5 minutes, the solution cooled and poured on ice, and the crude phenoxarsonic acid filtered off and washed. The pure *acid* crystallised from alcohol in small plates, m. p. 289—291° (Found: As, 23·2. $C_{13}H_{10}O_3ClAs$ requires As, 23·1%).

8 : 10-Dichloro-2-methylphenoxarsine.—The preceding phenoxarsonic acid (28 g.) was suspended in a mixture of concentrated hydrochloric acid and chloroform and reduced at 60° with sulphur dioxide in presence of a little iodine. When the reduction was complete, the suspension was cooled and submitted to filtration. The crude *chloroarsine* crystallised from alcohol, containing a little concentrated hydrochloric acid, in pale yellow needles, m. p. 171—172° [Found: Cl (attached to As), 11·1. $C_{13}H_9OCl_2As$ requires Cl, 10·8%].

8-Chloro-10-phenyl-2-methylphenoxarsine.—To the decanted Grignard reagent prepared from 66 g. of bromobenzene (6 mols.) were added 23 g. of 8 : 10-dichloro-2-methylphenoxarsine (1 mol.) suspended in benzene. The mixture was heated in boiling water for 7 hours, the ether being allowed to distil. The product was decomposed with ice and hydrochloric acid. The benzene solution was separated and dried, and the solvent removed. The residue was distilled in a vacuum and 23·g. (89% yield) of *arsine* were obtained, b. p. 258°/3 mm. It was a thick oil which crystallised when stirred with a little alcohol; recrystallised from the latter, it formed hexagonal plates, m. p. 75—76° (Found: As, 20·3. $C_{19}H_{14}OClAs$ requires As, 20·3%).

dl-*8-Chloro-10-phenylphenoxarsine-2-carboxylic Acid.*—A suspension of the foregoing arsine (23 g.) in a solution of 60 g. of potassium permanganate in 800 c.c. of water was boiled under reflux for 2 hours. Sulphur dioxide was passed into the resulting mixture and the oxide acid was precipitated. It was filtered off and purified through the sodium salt. The acid thus obtained was suspended in chloroform and reduced, after addition of dilute hydrochloric acid and a little iodine, by passage of sulphur dioxide through the mixture for 1 hour. The chloroform was allowed to evaporate completely and the precipitated *acid* was collected, crystallised from dilute alcohol, and recrystallised from glacial acetic acid, from which it separated in hexagonal plates, m. p. 220—221° (Found: C, 56·5; H, 2·8. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0%).

Resolution of dl-*8-Chloro-10-phenylphenoxarsine-2-carboxylic Acid.*—To a boiling solution of 10 g. of the *dl*-acid in 750 c.c. of ethyl alcohol were added 3 g. (1 mol.) of *d*-α-phenylethylamine. The solution was kept overnight and 5·6 g. of salt *A* were obtained having $[\alpha]_{5791}^{20°}$ − 5·3° in methyl alcohol. Concentration of the mother-liquor gave successive crops, 3·2 g. of *B* with $[\alpha]_{5791}^{20°}$ + 13·2°, 1 g. of *C* with $[\alpha]_{5791}^{20°}$ + 9·2°, 1·5 g. of *D* with $[\alpha]_{5791}^{20°}$ + 9·5°, and 1 g. of *E*

with $[\alpha]_{5791}^{20°}$ + 10·6°. Salt *A* was recrystallised four times from ethyl alcohol and thereafter the rotation remained constant and 1 g. of pure *d*-α-phenylethylamine *l*-acid was obtained. Salt *B* was recrystallised from methyl alcohol and a series of salts was obtained whose specific rotation varied from + 8·2° to + 17·7°. Repeated crystallisation from either methyl alcohol, dilute ethyl alcohol, or acetone did not effect a separation of the *d*-acid salt and the partial racemate. Salts *C*—*E* were combined and after a number of crystallisations the specific rotation remained constant at + 9·5°. Decomposition of these impure salts gave acids with small dextrorotations ($[\alpha]_{5791}^{20°}$ + 4·4° to + 8·4° in acetone).

In another experiment, to 10 g. of the *dl*-acid in 650 c.c. of ethyl alcohol was added *d*-α-phenylethylamine (⅓ mol.). 1·5 G. of salt separated having $[\alpha]_{5791}^{20°}$ − 61·0° in methyl alcohol. To the mother-liquor another ⅓ mol. of base was added and 4·5 g. of salt were obtained having $[\alpha]_{5791}^{20°}$ + 8·5°. Addition of another ⅓ mol. of base gave 0·9 g. of salt with $[\alpha]_{5791}^{20°}$ + 20·4°. Concentration of the mother-liquor gave salts with $[\alpha]_{5791}^{20°}$ + 8·5° to + 8·9° in methyl alcohol. Recrystallisation of the first crop from ethyl alcohol gave the pure *d*-α-phenylethylamine *l*-acid salt, but the other crops, as before, gave inseparable mixtures with approximately the same rotations of $[\alpha]_{5791}^{20°}$ + 9·5°. The resolution was repeated with *l*-α-phenylethylamine and when it was performed according to the second method described above the first crop which separated had $[\alpha]_{5791}^{20°}$ + 67·9° and this, after *one* recrystallisation from ethyl alcohol, was the pure *d*-acid salt. As before, the subsequent crops were inseparable mixtures.

d-α-*Phenylethylamine* 1-8-*chloro*-10-*phenylphenoxarsine*-2-*carboxylate* crystallised from ethyl alcohol in sheaves of rectangular plates, m. p. 236—237°. It had $[\alpha]_{5791}^{20°}$ − 71·7° and $[\alpha]_{5461}^{20°}$ − 85·4° in methyl alcohol (c = 0·627; l = 2; $\alpha_{5791}^{20°}$ = 0·90°, $\alpha_{5461}^{20°}$ = 1·07°) (Found: C, 62·3; H, 4·4. $C_{19}H_{12}O_3ClAs,C_8H_{11}N$ requires C, 62·4; H, 4·5%).

l-α-*Phenylethylamine* d-8-*chloro*-10-*phenylphenoxarsine*-2-*carboxylate* had $[\alpha]_{5791}^{20°}$ + 71·3° and $[\alpha]_{5461}^{20°}$ + 85·0° in methyl alcohol (c = 0·953; l = 2; $\alpha_{5791}^{20°}$ = + 1·36°, $\alpha_{5461}^{20°}$ = + 1·62°) (Found: C, 62·3; H, 4·4%).

The salts were decomposed by pouring methyl-alcoholic solutions into dilute hydrochloric acid, and the precipitated acids collected. 1-8-*Chloro*-10-*phenylphenoxarsine*-2-*carboxylic acid* crystallised from dilute ethyl alcohol in leaflets, m. p. 202—203°, $[\alpha]_{5791}^{20°}$ − 68·7° and $[\alpha]_{5461}^{20°}$ − 81·1° in acetone (c = 0·917; l = 2; $\alpha_{5791}^{20°}$ − 1·26°, $\alpha_{5461}^{20°}$ = − 1·50°) (Found: C, 57·0; H, 2·7. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0%). d-8-*Chloro*-10-*phenylphenoxarsine*-2-*carboxylic acid* crystallised from dilute alcohol in leaflets, m. p. 202—203°, $[\alpha]_{5791}^{20°}$ + 69·0° and $[\alpha]_{5461}^{20°}$ + 81·9° in acetone (c = 0·739; l = 2; $\alpha_{5791}^{20°}$ = + 1·02°, $\alpha_{5461}^{20°}$ = + 1·21°) (Found: C 57·2; H, 3·0%).

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