301. *The Configuration of Heterocyclic Compounds. Part III. The Optical Resolution of* 10-*Ethylphenoxarsine*-2-*carboxylic Acid.*

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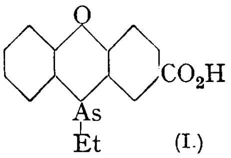
In view of the fact that 10-methylphenoxarsine-2-carboxylic acid was the only example of a phenoxarsine which exhibited optical activity (Lesslie and Turner, J., 1934, 1172), we regarded it as essential to prepare, and attempt the resolution of, a second compound of the same class. 10-*Ethylphenoxarsine*-2-*carboxylic acid* (I) has been synthesised by a method similar to that employed for the methyl acid. The strychnine salt was found to be most suitable for use, although, when an alcoholic solution of the acid was treated fractionally with this alkaloid, evidence of resolution was not immediately apparent. Addition of the equivalent of strychnine in three equal portions gave salts having identical rotations. When, however, these were combined and crystallised, a salt of much higher rotation was obtained. On concentration of the mother-liquor, a variety of crops were deposited, with first positive and then negative rotations. Concentration of the original mother-liquor gave strongly lævorotatory salts. The existence of three distinct salts was soon recognised, owing to the considerable difference in crystalline form, but the separation of the pure diastereoisomerides presented far more difficulty than was experienced with the methyl acid.



(I.)

Strychnine d-10-*ethylphenoxarsine*-2-*carboxylate* forms very sparingly soluble, rectangular needles, $[\alpha]^{20°}_{5791}$ + 49·2° and $[\alpha]^{20°}_{5461}$ + 57·4° in chloroform. The l-*salt*, very soluble, glistening plates, has $[\alpha]^{20°}_{5791}$ − 53·9° and $[\alpha]^{20°}_{5461}$ − 63·2°. The partial racemate, which was not isolated in the pure condition, forms characteristic spherical aggregates.

The optically pure 10-ethylphenoxarsine-2-carboxylic acids, obtained by decomposition of the strychnine salts and subsequent recrystallisation, have $[\alpha]^{20°}_{5791}$ ± 119·0° ± 0·3° and $[\alpha]^{20°}_{5461}$ ± 139·0° ± 0·5° in 99·7% alcohol.

A solution of the *d*-acid in *N*-sodium hydroxide, which originally had α_{5461} + 0·91° ($l = 2$; $c = 0·275$), was heated in a closed tube at 100°; after 4 hours α_{5461} was 0·90°, and after 9 hours 0·81°. The optical stability of the ions of the acid is therefore of the same order as that for the methyl acid.

A solution of the *d*-acid in alcoholic methyl iodide lost its activity slowly during 2 hours, and then much more rapidly : a similar period of induction was noticed with the methyl acid.

Experimental.

dl-10-*Ethylphenoxarsine*-2-*carboxylic Acid.*—10-Chlorophenoxarsine-2-carboxylic acid (Lesslie and Turner, *loc. cit.*) (22·4 g.; 1 mol.) was added gradually to the decanted Grignard reagent prepared from 65 g. of ethyl iodide (6 mols.). There was vigorous reaction on each addition. The clear solution was gently boiled for ½ hr., and then decomposed with ice and dilute hydrochloric acid. The aqueous layer was repeatedly extracted with ether, and the total ethereal solution was washed with water and then extracted several times with aqueous ammonia. On acidification of the latter, the *acid* was obtained in good yield. It crystallised (12 g.) from absolute alcohol in clusters of needles, m. p. 162—163° with slight previous softening (Found : C, 57·0; H, 4·1; As, 24·0. $C_{15}H_{13}O_3As$ requires C, 56·9; H, 4·15; As, 23·7%).

Resolution. To a boiling solution of 18 g. of the acid in about 1 l. of 99·7% ethyl alcohol were added 6·3 g. of strychnine (0·33 mol.). After standing over-night in the ice-chest, the solution deposited 1·1 g. of salt having $[\alpha]^{20°}_{5791}$ + 12·8° in chloroform. To the hot mother-liquor were added another 6·3 g. of strychnine, and 11 g. of salt were obtained, having $[\alpha]^{20°}_{5791}$ + 13·0°. The remaining 6·3 g. of strychnine were added, and 10 g. of salt were obtained, having $[\alpha]^{20°}_{5791}$ + 13·2°. These three crops were combined and recrystallised from 3 l. of alcohol, 6·6 g. of salt being obtained with $[\alpha]^{20°}_{5791}$ + 29·2°. Successive concentrations of the mother-liquor gave a series of salts having specific rotations varying from + 25·0° to − 12·2°. The original mother-liquor on concentration gave a series of salts of specific rotation − 38·1° to − 52·2°. All the dextrorotatory salts were separately recrystallised several times, until the specific rotation was about + 45·0°. They were then combined, and after recrystallisation four times, the pure strychnine *d*-salt was obtained. The lævorotatory salts were treated similarly, but in this case the first crop obtained in all the crystallisations contained partial racemate, and the optically purer *l*-acid salt could only be obtained by concentration of the mother-liquor, followed by repetition of the same process, until the specific rotation was about − 52°. Thereafter, no more partial racemate separated, and recrystallisation was continued until the specific rotation remained constant.

Strychnine d-10-*ethylphenoxarsine-2-carboxylate* crystallises in rectangular needles from alcohol, in which it is very sparingly soluble. It melts at 247—248° (decomp.) and has $[\alpha]^{20^\circ}_{5791}$ + 49·2°, $[\alpha]^{20^\circ}_{5461}$ + 57·4° in chloroform ($l = 2$; $c = 1·882$; $\alpha_{5791} = + 1·85°$; $\alpha_{5461} = + 2·16°$) (Found : C, 66·4; H, 5·6. $C_{36}H_{35}O_5N_2As$ requires C, 66·5; H, 5·4%). The l-*isomeride* crystallises in thin plates from alcohol, in which it is very soluble. It melts at 188—189° (decomp.) and has $[\alpha]^{20^\circ}_{5791}$ − 53·9°, $[\alpha]^{20^\circ}_{5461}$ − 63·2° in chloroform ($l = 2$; $c = 1·947$; $\alpha_{5791} = − 2·10°$; $\alpha_{5461} = − 2·46°$) (Found : C, 66·2; H, 5·6%).

The salts were decomposed in the usual manner with ammonia, and the free acids obtained. d-10-*Ethylphenoxarsine-2-carboxylic acid* crystallises in very slender needles from aqueous alcohol, in which it is very soluble; m. p. 128—129°, $[\alpha]^{20^\circ}_{5791}$ + 119·2°, $[\alpha]^{20^\circ}_{5461}$ + 139·5° in alcohol ($l = 2$; $c = 0·889$; $\alpha_{5791} = + 2·12°$; $\alpha_{5461} = + 2·48°$) (Found : C, 57·1; H, 4·3. $C_{15}H_{13}O_3As$ requires C, 56·9; H, 4·15%). The l-*acid* crystallises similarly, m. p. 128—129°, $[\alpha]^{20^\circ}_{5791}$ − 118·8°, $[\alpha]^{20^\circ}_{5461}$ − 138·5° in alcohol ($c = 0·202$) (Found : C, 57·4; H, 4·45%).

Action of Alcoholic Methyl Iodide on the d-*Acid.*—A solution (20 c.c.) of 0·0622 g. of the acid and 2 c.c. of methyl iodide in absolute alcohol was kept in a polarimeter tube, and the following observations made :

t (mins.)	0	35	140	180	220	250	290	320	∞
α_{5791} …………	+0·70°	0·70°	0·62°	0·52°	0·39°	0·22°	0·09°	0·04°	0·00°
α_{5461} …………	+0·81°	0·81°	0·74°	0·62°	0·44°	0·25°	0·10°	0·05°	0·00°

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