256. *The Configuration of Heterocyclic Compounds. Part XII. The Optical Resolution of* 2-*Chloro*-10-p-*carboxyphenylphenoxarsine.*

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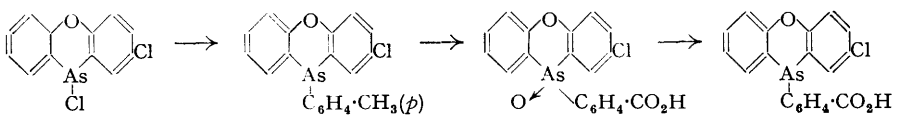
2-Chloro-10-*p*-carboxyphenylphenoxarsine has been resolved by means of the strychnine and cinchonine salts. The active acids, $[\alpha]_{5791}^{20°}$ +162·1° and −161·3° in chloroform, showed high optical stability.

In Part XI of this series (Campbell, *J.*, 1947, 4) the resolution of 10-*p*-carboxyphenyl-2-methylphenoxstibine was described. The active acids were found to undergo racemisation in boiling alcohol whereas the optically active phenoxarsines (Lesslie and Turner, *J.*, 1934, 1170; 1935, 1268; 1936, 730; Lesslie *J.*, 1938, 1001) had shown high optical stability. It was suggested by Campbell that one of the factors contributing to the optical instability of the phenoxstibine might be the heavy polar *p*-carboxyphenyl group in the 10-position which might encourage inversion of the pyramidal configuration of the antimony atom. It therefore seemed desirable to prepare a similar 10-*p*-carboxyphenylphenoxarsine to see if the optical stability of the phenoxarsine was affected. 2-*Chloro*-10-p-*carboxyphenylphenoxarsine* was synthesised, and a number of its alkaloidal salts were examined. The (±)-acid was prepared according to the following scheme:



The strychnine salt crystallised from a 1 : 1 mixture of chloroform and alcohol, and after repeated recrystallisation from the same solvent the optically pure strychnine (+)-acid *salt*, $[\alpha]_{5791}^{20°}$ +69·7° and $[\alpha]_{5461}^{20°}$ +80·7° in chloroform, was obtained. The *acid* regained from this salt had $[\alpha]_{5791}^{20°}$ +162·1° and $[\alpha]_{5461}^{20°}$ +187·5°. The more soluble strychnine salt was recrystallised from alcohol until the rotation was constant, $[\alpha]_{5791}^{20°}$ −100·6° and $[\alpha]_{5461}^{20°}$ −115·3°, but the acid obtained from it, $[\alpha]_{5791}^{20°}$ −128·3° and $[\alpha]_{5461}^{20°}$ −148·3° in chloroform, was not optically pure.

The quinine salts were examined, but again complete separation of the diastereoisomers could not be effected. The more sparingly soluble (−)-acid salt was recrystallised 8 times from alcohol; the rotation was then constant $[\alpha]_{5791}^{20°}$ −177·2° and $[\alpha]_{5461}^{20°}$ −203·4° in chloroform. The acid obtained from this salt, however, had $[\alpha]_{5791}^{20°}$ −138·0° and $[\alpha]_{5461}^{20°}$ −159·6°. No attempt was made to purify the more soluble (+)-acid salt.

The optically impure (−)-acid was converted into the cinchonine salt, and after 13 recrystallisations from alcohol the optically pure cinchonine (−)-acid *salt* had $[\alpha]_{5791}^{20°}$ −12·3° and $[\alpha]_{5461}^{20°}$ −15·9° in chloroform. The acid regenerated from this salt had $[\alpha]_{5791}^{20°}$ −161·3° and $[\alpha]_{5461}^{20°}$ −187·1°.

During the above resolution experiments there was no indication that prolonged boiling in alcoholic solution of any of the alkaloidal salts led to asymmetric transformation (cf. Campbell, *J.*, 1947, 4). The active acids were also unaffected when their solutions in either chloroform or alcohol were boiled for 1 hour. After a solution of the (+)-acid in 0·5N-sodium hydroxide had been boiled for 3 hours the rotation of the recovered acid was unchanged. The optical stability of the phenoxarsines would therefore appear to be unaffected by the *p*-carboxyphenyl group in the 10-position.

Experimental.

Carbon and hydrogen analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. Rotations were observed in chloroform in 2 dm. tubes.

2 : 10-*Dichlorophenoxarsine.*—This substance was synthesised by the method of Roberts and Turner (*J.*, 1925, 2004) by reduction of 2-chlorophenoxarsonic acid. The acid (50 g.) was suspended in a mixture of concentrated hydrochloric acid and chloroform containing a little iodine, and reduced at 50° by passing in sulphur dioxide. The product was a mixture of 2 : 10-dichlorophenoxarsine, m. p. 144—145°, and 2-*p*-chlorophenoxyphenyldichloroarsine, m. p. 67—68° (*J.*, 1925, 2004), in the ratio 2 : 1. Separation was effected by crystallisation from chloroform in which solvent the dichlorophenoxarsine was the more sparingly soluble. Reduction of the chloroform mother-liquor gave crude 2-*p*-chlorophenoxyphenyldichloroarsine which was purified by crystallisation from light petroleum (b. p. 60—80°). It was converted into the required 2 : 10-dichlorophenoxarsine by distillation under reduced pressure. The above reduction was repeated several times, and always resulted in a mixture of the two chloroarsines being obtained. Roberts and Turner reported an arsenic-free substance isolated from their reduction product, but in the above reductions no trace of it was evident.

2-*Chloro*-10-p-*tolylphenoxarsine.*—To the decanted Grignard reagent prepared from *p*-bromotoluene (208 g.; 4 mols.) was added a solution in benzene (300 c.c.) of 2 : 10-dichlorophenoxarsine (95 g.; 1 mol.). The solution was heated in boiling water for 9 hours, the ether being allowed to distil gradually. The product was decomposed with ice and dilute hydrochloric acid. The benzene solution was separated, washed, and dried, and the solvent removed. The residue was distilled in a vacuum, and 88 g. (80% yield) of the *arsine* were obtained as a viscous oil, b.p. 260—264°/10 mm. It crystallised on being stirred with a mixture of acetone and light petroleum. It was recrystallised from alcohol; needles, m. p. 70—71° (Found : C, 61·5; H, 4·1; As, 20·6. $C_{19}H_{14}OClAs$ requires C, 61·9; H, 3·8; As, 20·3%).

2-*Chloro*-10-p-*carboxyphenylphenoxarsine* 10-*Oxide.*—The foregoing arsine (30 g.) was suspended in a solution of potassium permanganate (30 g.) in water (800 c.c.), and the mixture boiled under reflux for 3 hours. Sulphur dioxide was then passed into the solution, and the *oxide-acid* was precipitated. It was collected and purified through the sparingly soluble sodium salt. Crystallised from glacial acetic acid it formed rectangular prisms, m. p. 325—326° (Found : C, 54·7; H, 2·9; As, 18·1. $C_{19}H_{12}O_4ClAs$ requires C, 55·0; H, 2·9; As, 18·1%).

2-*Chloro*-10-p-*carboxyphenylphenoxarsine.*—The preceding oxide-acid (33 g.) was suspended in dilute hydrochloric acid and chloroform containing a little iodine; sulphur dioxide was passed into the warmed mixture for about 1½ hours, the chloroform being allowed to evaporate gradually but completely. The *acid* was collected and crystallised from alcohol, needles (25 g.), m. p. 226—227°, being obtained (Found : C, 57·2; H, 3·2; As, 18·8. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0; As, 18·8%).

Resolution with Strychnine.—To the (±)-acid (12 g.) dissolved in boiling alcohol (500 c.c.) was added a solution of strychnine (10 g.) in warm chloroform (100 c.c.). The first fraction *A* (7 g.) which separated overnight had $[\alpha]_{5791}^{20°}$ +49·3° (*c*, 0·902). The mother-liquor was reduced to 450 c.c., and a second crop *B* (7·9 g.) separated which had $[\alpha]_{5791}^{20°}$ −16·9° (*c*, 1·124). On further reduction of the mother-liquor to 200 c.c. a third crop *C* (5·5 g.) was obtained which had $[\alpha]_{5791}^{20°}$ −99·5° (*c*, 1·126). Salt *A* was recrystallised 4 times from alcohol–chloroform and thereafter remained constant in rotation. Salt *B* was recrystallised several times from the same solvent until it was optically pure. 4·5 G. of strychnine (+)-acid *salt* were obtained having $[\alpha]_{5791}^{20°}$ +69·7° and $[\alpha]_{5461}^{20°}$ +80·7° (*c*, 1·055). It crystallised in clumps of small needles, m. p. 249—250° (Found : C, 64·9; H, 4·8. $C_{40}H_{34}O_5N_2ClAs$ requires C, 65·5; H, 4·7%).

The above salt was decomposed by stirring with dilute hydrochloric acid. (+)-2-*Chloro*-10-p-*carboxyphenylphenoxarsine* crystallised from alcohol in very slender needles, m. p. 219—220°. It had $[\alpha]_{5791}^{20°}$ +162·1° and $[\alpha]_{5461}^{20°}$ +187·5° (*c*, 0·944) (Found : C, 57·2; H, 2·9. $C_{19}H_{12}O_3AsCl$ requires C, 57·2; H, 3·0%). Salt *C* after a number of recrystallisations from alcohol had constant rotation, $[\alpha]_{5791}^{20°}$ −100·6° and $[\alpha]_{5461}^{20°}$ −115·3° (*c*, 0·984); nevertheless, the acid recovered from this salt had $[\alpha]_{5791}^{20°}$ −128·3° and $[\alpha]_{5461}^{20°}$ − 148·3° (*c*, 0·998), and it was obvious that the (−)-acid salt and the partial racemate could not be separated. All the fractions of optically impure salt were decomposed with dilute hydrochloric acid, and after crystallisation from alcohol the recovered acid had $[\alpha]_{5791}^{20°}$ −37·4° and $[\alpha]_{5461}^{20°}$ −42·5° (*c*, 1·471).

Attempted Resolution with Quinine.—The acid ($[\alpha]_{5791}^{20°}$ −37·4°) (7·3 g.) and quinine (5·9 g.) were dissolved in boiling alcohol (400 c.c.); during the night 7·6 g. of salt separated in rosettes of sheaves of fine needles, having $[\alpha]_{5791}^{20°}$ −129·5° and $[\alpha]_{5461}^{20°}$ −149·7° (*c*, 0·994). After 6 recrystallisations from alcohol the rotation remained constant, $[\alpha]_{5791}^{20°}$ −177·2° and $[\alpha]_{5461}^{20°}$ −203·4° (*c*, 1·064). The salt was decomposed with dilute hydrochloric acid, and after crystallisation from alcohol the acid had $[\alpha]_{5791}^{20°}$ −133·9° and $[\alpha]_{5461}^{20°}$ −156·3° (*c*, 1·075). Recrystallisation of the acid did not affect the rotation.

Resolution with Cinchonine.—The acid ($[\alpha]_{5791}^{20°}$ −133·9°) (4·95 g.) and cinchonine (3·6 g.) were dissolved in boiling alcohol (130 c.c.). The solution after standing overnight deposited 6·9 g. of salt having $[\alpha]_{5791}^{20°}$ +17·9° and $[\alpha]_{5461}^{20°}$ +19·3° (*d*, 1·087). It was recrystallised 13 times from alcohol, and the rotation by then remained constant. The cinchonine (−)-acid *salt* crystallised in small rods, m.p. 139—140°, $[\alpha]_{5791}^{20°}$ −12·3° and $[\alpha]_{5461}^{20°}$ −15·9° (*c*, 0·972) (Found : C, 65·5; H, 5·0. $C_{38}H_{34}O_4N_2ClAs$ requires C, 65·8; H, 4·9%). (−)-2-*Chloro*-10-p-*carboxyphenylphenoxarsine* crystallised from alcohol in slender needles, m. p. 219—220°. It had $[\alpha]_{5791}^{20°}$ −161·3° and $[\alpha]_{5461}^{20°}$ −187·1° (*c*, 0·930) (Found : C, 57·5; H, 3·1. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0%).

The active acids were sensitive to light, and on exposureto sunlight became pink. This sensitivity was not observed in the racemic acid.

0·2 G. of pure (+)-acid were boiled under reflux with 0·5N-sodium hydroxide for 3 hours. The crude acid recovered had $[\alpha]_{5791}^{20°}$ +161·6° and $[\alpha]_{5461}^{20°}$ +187·2° (*c*, 0·956).

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